Abstracts of Scientific Papers
1990 Annual Meeting

Volume 70, Number 2S, February 1990

Anesthesia and Analgesia

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Yours sincerely,

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(atracurium besylate)

Brief Summary
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WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome.

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:
Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2°to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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[1] Payne J: Atracurium in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects.* Orlando, Grune & Stratton, 1984, p 98.

[2] d'Hollander A, Luyckx C, Eravis L: Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: Lack of age-related effects. *Anesthesia* 1983;59:237-240.

[3] Duvaldestin P, Saada J, Berger JL, et al: Pharmacokinetics, pharmacodynamics and dose response relationships of pancuronium in control and elderly subjects. *Anesthesia* 1982;56:36-40.

[4] d'Hollander A, Massaux F, Nevelsteen M: Age-dependent dose-response relationship of Org NC45 in anesthetized patients. *Br J Anaesth* 1982;54:653-657.

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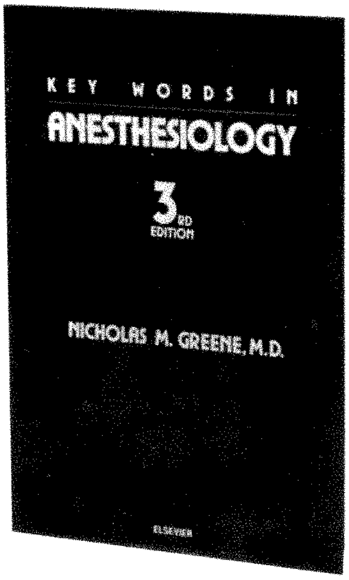

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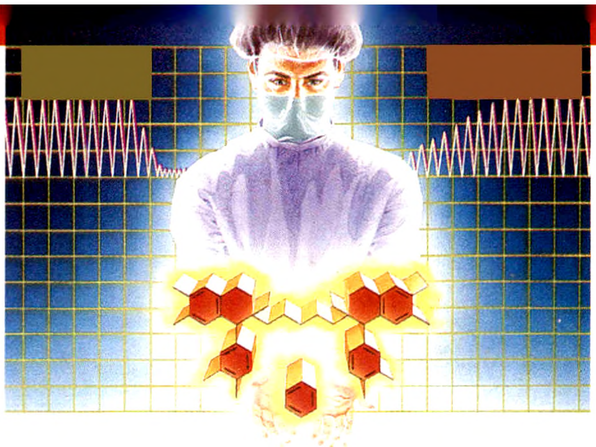

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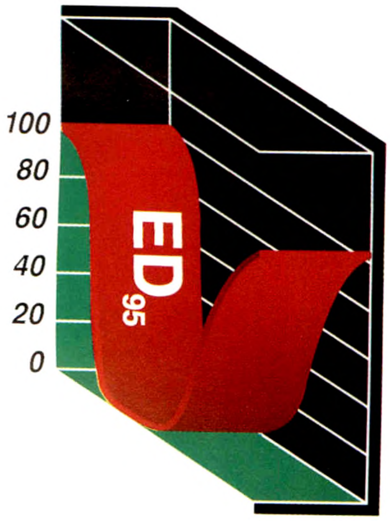

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Anesthesia
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Abstracts of Papers and Posters Presented at the International Anesthesia Research Society 64th Congress

Honolulu, Hawaii
March 9–13, 1990

Abstracts:	S1–S450
Author Index:	S451–S468
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Journal of the International Anesthesia Research Society

Title: A CURVED NEEDLE TECHNIQUE FOR CELIAC PLEXUS AND LUMBAR SYMPATHETIC BLOCK

Authors: A.R. Abadir, MD; J.H. Silverstein, MD; D. Sider, MD

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Introduction: The technique for celiac plexus and lumbar sympathetic blocks was introduced by Mandl in 1926. The classic technique employs a standard straight needle which is inserted from a position 10-12cm lateral to the midline. We have developed a technique which provides a greater degree of control over the tip of the needle, greatly facilitates placement of the needle tip at the proper location and minimizes the potential for pleural, lung, great vessel and solid organ injury.

Methods: Informed consent was obtained from all patients prior to the procedure.
An 12.5 cm 20 gauge spinal needle or an 12.5 cm Touhey needle is bent into a arc subtending an angle of 100 degrees. In this form, control of the needle tip is essentially opposite that of a straight needle.(Figs 1 and 2). With the needle fixed in tissue, elevating the hub of the needle elevates the tip, and vice versa.

The patient is positioned in the lateral decubitus position on the table. For lumbar sympathetic blockade a point 4-5cm lateral to the midline at the level of the lower third of L2(1) is located. Following the administration of local anesthesia, the needle is inserted perpendicular to the skin and advanced in a curvilinear direction to the anterior border of the vertebral body. To advance the tip of the needle to the sympathetic chain(fig 3), the hub of the needle is elevated(fig 2) and advanced slowly. The needle is aspirated repetitively to detect inadvertent intravascular placement. Loss of resistance and contrast radiography using a C-arm image intensifier are used to confirm the position of the needle prior to injection, particularly if a neurolytic agent is to be used.

Results: 51 lumbar sympathetic blocks and 16 celiac plexus blocks have been performed utilizing this technique. In each case the block was successfully completed with a single needle insertion. No difficulty in positioning the needle tip in the immediate vicinity of the desired ganglion was encountered. No complications have arisen from this technique.

Discussion: Lumbar and celiac plexus blocks have become a widely used part of the pain clinicians armementarium. Since the original description of the technique various refinements have been reported including the use of single needle techniques(2,3). Cherry and Rao reported on a series of 20 cadavers in which the straight needle only transversed the kidney once(4). Brown and Kunjappan suggest that the block be performed at the L4 level in order to avoid injuring the kidney. Carron has stated, however, that the L2 location requires less anesthetic or neurolytic agent for successful blockade as the preganglionic outflow to the sympathetic chain ends at L2. Our technique, by maintaining close proximity to the vertebral body, significantly lessens the possibility of injuring a solid organ. In addition, although our technique requires a different form of manipulation of the needle, once mastered provides an extraordinarily simple means of locating the lumbar sympathetic or celiac plexus. In the instance of an exaggerated lateral diameter of the vertebral body, the curved needle provides a significant advantage in placement of medication near to the celiac plexus or lumbar sympathetic ganglion.

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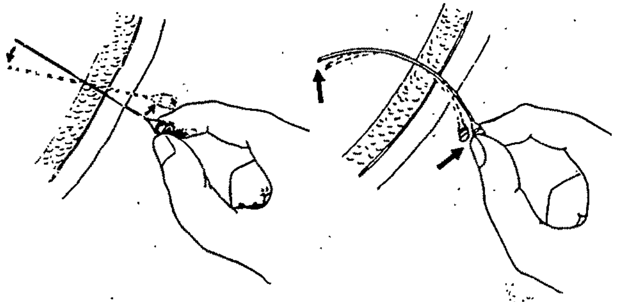

Figure 1: Figure 2:
Configuration of needles and mechanics of manipulation

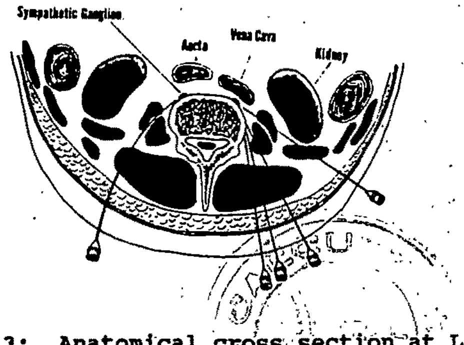

Figure 3: Anatomical cross section at L4 level demonstrating needle placement

Title: SKELETAL MUSCLE PO_2 ASSESSMENT DURING KETAMINE ANESTHESIA IN SHEEP

Authors: S. Abdi, M.D., G.I.J.M. Beerthuizen, M.D., D.N. Herndon, M.D., D.L. Traber, Ph.D.

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Introduction: Ketamine is a widely employed anesthetic drug for surgical procedures and intensive care patients. There are several publications regarding the hemodynamic responses to ketamine (1-3). However, little data are available concerning its influence on the peripheral circulation. Therefore, the purpose of our present study was to investigate the effects of ketamine on peripheral circulation.

Methods: Sheep (n=6) were chronically instrumented with femoral arterial and Swan-Ganz catheters. Five days after recovery from the surgical procedures, baseline data were collected: hemodynamic, respiratory parameters and skeletal muscle PO_2 using a polarographic needle electrode as an index of peripheral tissue perfusion. The animals received a bolus injection of ketamine (3 mg/kg) and measurements were taken at 5, 15, 30 and 60 min post injection. The experiment was then repeated using ketamine at a bolus dose of 6 mg/kg intravenously.
The experiment was approved by the institutional animal investigation committee.
Friedman's non-parametric analysis of variance was used to identify statistical significant changes.
Results: The results of our study are summerized in fig.1 and tab.1. A significant decrease of arterial pH, mixed venous pH, skeletal muscle PO2, but an increase in mean arterial blood pressure (MAP) was found in both dosages.

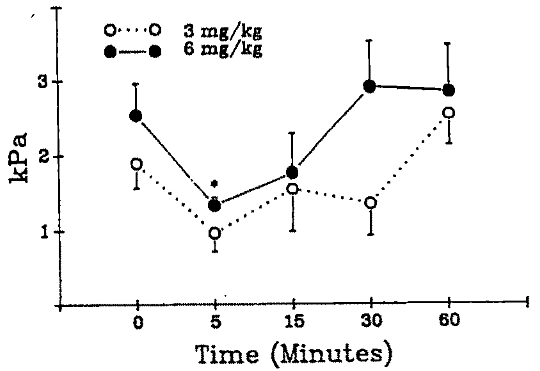
Table 1.

	3mg/kg		6mg/kg	
TIME	0	5	0	5
MAP	104±7	116±6*	103±4	119±9*
HR	84±6	84±8	78±5	73±4
CI	5.55±0.24	5.77±0.25	5.81±0.34	5.40±0.22
TPRI	1513±50	1624±77	1443±87	1773±135*
pHa	7.47±0.01	7.41±0.01	7.45±0.02	7.38±0.01*
pHv	7.42±0.01	7.30±0.05*	7.42±0.01	7.35±0.01*

MEAN ± S.E.M. * $p < 0.05$

Figure 1

Effect of Ketamine on Skeletal Muscle PO_2



Mean ± S.E.M * differs from baseline (p<0.05)

Discussion: This study shows that ketamine induced an increase in total peripheral vascular resistance index (TPRI) resulting in a decreased peripheral perfusion as indicated by a decrease in skeletal muscle PO_2, decreased arterial and mixed venous pH. These suggest that ketamine influences the microcirculation which might be a significant factor to consider when using it for patients in intensive care units or in operating rooms.

(Supported by NIH grant #GM33324)

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TITLE: PULMONARY VEIN AND MITRAL FLOW VELOCITIES PREDICT CHANGES IN HEMODYNAMICS

AUTHORS: MD Abel, M.D., RA Nishimura, M.D.
AFFILIATION: Department of Anesthesiology and Department of Internal Medicine, Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota 55905

Introduction. If transesophageal echocardiography (TEE) is to become an alternative, less invasive, monitor to pulmonary artery catheterization in the operating room, it will have to provide information about contractility and filling pressures. Doppler-derived mitral flow velocity provides information about diastolic filling of the heart which may allow a prediction of filling pressures.[1] Predictable changes in the mitral flow velocity that develop under varying loading conditions[2] provide a conceptual framework for the interpretation of transmitral velocity curves obtained in different conditions.[3] In this study we attempted to relate changes in pulmonary vein and mitral flow velocities to hemodynamic changes during different loading conditions. This study was performed in supine, anesthetized patients prior to coronary revascularization. Loading conditions were modified in a systematic manner.

Methods. This study was approved by the Institutional Review Board. Nine patients (mean age 77 ± 10 yrs) were studied. All patients had a left ventricular ejection fraction > 40%, with a mean of 56 ± 13%, and none had valvular heart disease. Patients were excluded if they had unstable angina, unstable hemodynamics, or left main coronary artery stenosis. Patients were monitored with TEE and a pulmonary artery catheter. Transmitral velocity was measured at the tips of the mitral valve leaflets to achieve the highest velocity. Velocity in the left upper pulmonary vein was obtained as it emptied into the left atrium by placing the sample volume 1-2 cm into the pulmonary vein from its junction with the left atrium. All measurements were obtained prior to sternotomy and were obtained as follows: 1) baseline - approximately 30 min after induction of anesthesia; 2) during nitroglycerin (NTG) infusion to decrease the systolic blood pressure (SBP) by at least 20%; 3) during phenylephrine (PE) infusion to raise SBP by 20%; 4) following a crystalloid infusion (1 L) to increase the pulmonary capillary wedge pressure (PCWP) by at least 20% above baseline. Three consecutive mitral and pulmonary vein velocity curves were analyzed for each given period. Hemodynamic and Doppler values during each intervention were compared to the control state using a paired T test. Hemodynamic and Doppler parameters were compared using a linear regression analysis.

Results. Tables 1, 2, and 3 show the hemodynamic and Doppler data obtained during different loading conditions. The change in systolic velocity (S) in the pulmonary vein correlated directly with the change in cardiac output (CO) ($r = .62$, $p < 0.001$). There was a direct correlation between the atrial (A) velocity of the pulmonary vein and PCWP ($r = .81$, $p < 0.001$). A direct correlation between the mitral E velocity and the PCWP also was present ($r = .74$, $p < 0.001$).

Discussion. Use of transesophageal echocardiography has provided an excellent window for obtaining both pulmonary vein and mitral velocities by pulsed-wave Doppler echocardiography. In this study we demonstrated that predictable changes occur in pulmonary vein and mitral flow velocities which correlate with changes in left ventricular filling pressure. We believe that examination of pulmonary vein velocities in conjunction with mitral velocities provide a more complete assessment of the filling characteristics of the left side of the heart. In the future it may be possible to predict filling pressures from an assessment of these Doppler parameters using TEE without resorting to the more invasive use of pulmonary artery catheterization.

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Table 1. Hemodynamic Variables (mean ± SD)

	SBP (mmHg)	PCWP (mmHg)	CO (l/min)	HR (bpm)
Control	118 ± 16	11 ± 3	5.1 ± 1.1	60 ± 11
NTG	91 ± 13†	8 ± 2*	4.9 ± 0.9	61 ± 11
PE	151 ± 4†	15 ± 6	4.5 ± 0.7	54 ± 9*
Fluids	140 ± 13*	21 ± 4†	6.6 ± 1.1	60 ± 10

*$p < 0.05$
†$p < 0.001$

Table 2. Doppler Parameters (mean ± SD)

	Pulmonary Vein		
	S (m/s)	D (m/s)	A (m/s)
Control	.38 ± .14	.32 ± .12	.21 ± .07
NTG	.35 ± .15	.24 ± .05*	.12 ± .07†
PE	.36 ± .19	.27 ± .09	.21 ± .08
Fluids	.50 ± .24*	.42 ± .17†	.30 ± .08†

*$p < 0.05$
†$p < 0.001$
S = maximum systolic antegrade velocity
D = maximum diastolic antegrade velocity
A = velocity at atrial contraction

Table 3. Doppler Parameters (mean ± SD)

	Mitral Valve		
	E (m/s)	A (m/s)	DT (ms)
Control	.56 ± .09	.52 ± .11	218 ± 22
NTG	.46 ± .10*	.53 ± .11	296 ± 73*
PE	.51 ± .09	.54 ± .15	280 ± 88
Fluids	.73 ± .09*	.61 ± .16*	148 ± 34*

*$p < 0.05$
E = maximum diastolic velocity
A = velocity at atrial contraction
DT = deceleration time

Title: SUBARACHNOID MORPHINE PROLONGS LABOR COMPARED TO EPIDURAL BUPIVACAINE

Authors: E. Abouleish, M.D., N. Rawal, M.D., J. Shaw, M.D., M.N. Rashad, M.D., PhD., T. Lorenz, M.D.
Affiliation: Anesth. Departments, Univ. of Texas at Houston, Baylor College of Medicine, Houston, Tx. 77030

INTRODUCTION. Intrathecal morphine (I.T.) in a dose of 0.5 to 2 mg has been used for pain control during labor. However, a dose of 0.3 mg or more carries the risk of respiratory depression.^{1} Therefore, a dose less than 0.3 mg morphine is preferable. Epidural bupivacaine 0.125% is considered to be also effective.^{2} This study was conducted to compare the efficacy and side effects of 0.2 mg I.T. morphine with 0.125% epidural bupivacaine for labor pains.

METHODS. The study consisted of 62 parturients who were randomly divided into 3 groups: Group I (n=20) received 0.2 mg I.T. morphine, Group II (n=22) had 10 ml epidural bupivacaine 0.125%, and Group III (n=20) received both. All patients were full-term, of Physical Status ASA I, and carrying a normal fetus with cephalic presentation. The study was approved by the University and Hospital Human Research Committees and all patients gave written consents. Pain relief was evaluated periodically using a visual analogue score where 10 indicating maximum pain. Forty minutes following the initial injection of medication, repeated doses of 10-ml increments of 0.125% bupivacaine were injected epidurally as required to keep all patients comfortable. Vital signs were monitored intrapartum and every hour postpartum. Pulse oximetry was continuously used for 24 hours. For statistical analysis, chi square and analysis of variance were used; data were expressed as means ± SEM with statistical significance at $p < 0.05$.

RESULTS. There were no significant differences among the groups regarding age, gravidity, parity, gestational age, incidence of fetal distress, cesarean section rate, neonatal weight or Apgar Scores. Neither 0.2 mg I.T. morphine nor 10 ml 0.125% epidural bupivacaine alone provided adequate analgesia since the majority of these patients required supplementation at 40 minutes (Figure 1). The combination of the two drugs in the above-mentioned concentration produced excellent analgesia. Although cervical dilation and effacement, fetal head position, fetal head presentation, and the use of oxytocin were comparable in all groups, the first stage of labor, the total duration of labor, and the time from analgesia request to delivery were all prolonged when I.T. morphine was administered (table 1). There was no respiratory depression (respiratory rate ≤ 10 and $SaO_2 \leq 35\%$) in any group, but pruritus, nausea, and vomiting were more frequent with morphine administration. Urinary retention was more frequent with morphine, but not statistically significant. One patient in the combination group had spinal headache which responded to conservative treatment.

DISCUSSION. The prolongation of labor associated with I.T. morphine may be due to its action on the spinal cord centers controlling uterine contractility or to central depression of endogenous oxytocin secretion.^{3} The effect of I.T. morphine on the course of labor requires further investigations to define its mechanism. Our conclusion is that minidose I.T. morphine and low concentration of epidural bupivacaine, although individually ineffective, their combination in the doses described, provides excellent analgesia. However, our unexpected finding of prolongation of labor with I.T. morphine is a major disadvantage.

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Table 1
The Effect of Intrathecal Morphine on the duration of Labor

	Morphine (n=20)	Bupivacaine (n=22)	Combination (n=20)
Duration of first stage (hr)	11 ± 2.5	o ± 1.0*	10.5 ± 0.9
Duration of second stage (hr)	1.1 ± 0.3	0.5 ± 0.1	1 ± 0.2
Total duration of labor (hr)	12.6 ± 2.8	6.4 ± 1.1*	11.5 ± 1
Analgesia-request-to-delivery time (hr)	5.5 ± 0.9	3.5 ± 0.7*	6.1 ± 0.7

*Significantly shorter than the other 2 groups, P < .05

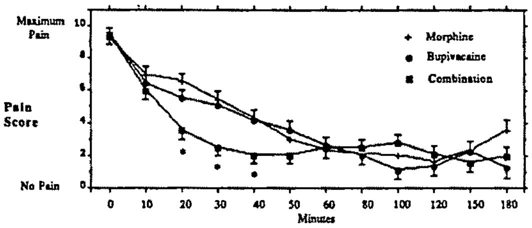

Figure. The effect of 0.2 mg intrathecal morphine, 0.125% epidural bupivacaine, and combination of both on pain score. * Statistically significant ($p<0.05$)

Title: DEXMEDETOMIDINE MAY REDUCE ISOFLURANE REQUIREMENTS DURING ABDOMINAL HYSTERECTOMY

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Introduction: A novel alpha$_2$-agonist, dexmedetomidine, has been shown to have sedative effects in human volunteers,[1] and its close imidazole derivative, detomidine is used as a sedative analgesic in veterinary medicine.[2] Dexmedetomidine diminishes dose-dependently halothane MAC in rats through a postsynaptic alpha$_2$-adrenergic receptor.[3] Dexmedetomidine was well tolerated in human volunteers,[4] and it is more selective alpha$_2$-adrenergic agonist than clonidine. Therefore, it might be useful as an anesthetic adjuvant or as a preanesthetic agent by potentiating the effects of narcotics and by reducing the dose requirements of inhalation anesthetics.

Methods: The study comprised 96 healthy 32-55 years old women (ASA I) undergoing elective abdominal hysterectomy. The study protocol was approved by the Ethical Committee of the hospital and the patients gave written informed consent for the study. The women were randomly allocated into four groups, each containing 24 patients. Every patient was premedicated with oral diazepam 0.1 mg.kg^{-1}, 45-60 min before the induction of anesthesia. On arrival in the operation theatre, a peripheral intravenous infusion of Ringer's solution was started, and the test drug was administered in double blind random fashion. The women in the study groups received dexmedetomidine hydrochloride, 0.3 or 0.6 μg.kg^{-1}, intravenously 10 min before the induction of anesthesia, and the women in the control groups, were given either fentanyl, 2 μg.kg^{-1}, or saline intravenously instead of dexmedetomidine. Sedation scores (1=awake, eyes open, 2=asleep, easy to arouse, 3=asleep, difficult to arouse) were estimated 2, 5 and 8 min after administering the test dose. Ten minutes after the administration of the test drugs, prior to the induction of anesthesia, the patients were given glycopyrrolate, 0.2 mg i.v., and vecuronium bromide, 0.6 mg i.v. Anesthesia was induced with thiopental, 4 mg.kg^{-1}. Succinylcholine,1 mg.kg^{-1}, was given to facilitate endotracheal intubation. For further relaxation vecuronium bromide was administered to achieve and maintain 80% relaxation. Anesthesia was started with 0.3% (end tidal) isoflurane (Forene, Abbot) in nitrous oxide (70%) and oxygen. Thereafter, the isoflurane concentration was adjusted to keep blood pressure and heart rate within 20% limits of the preoperative values, in order to administer the lowest possible isoflurane concentration during the operation. Fentanyl was given, in 0.05 mg increments, if the end-tidal isoflurane concentration exceeded 1.5%. The total isoflurane concentration, needed, was counted using the means of 20 min periods during the procedure.

Results: Patient charateristics and the main results are shown in Table 1. Five min after administering dexmedetomidine, 0.6μg.kg $^{-1}$ or fentanyl 2.0 μg.kg^{-1}, the patients were more sedated than those in the placebo group. After laryngoscopy and endotracheal intubation the maximal increase in the blood pressure and in the heart rate were lower in the women premedicated with the higher dose of dexmedetomidine compared to those in the placebo group. Also fentanyl attenuated the increase in systolic blood pressure, but not the increase in the heart rate. In the women premedicated with dexmedetomidine, 0.3 μg.kg^{-1}, the increase in blood pressure and heart rate did not differ from the placebo group. In the women who had received the higher dose of dexmedetomidine, 0.6 μg.kg^{-1}, the mean isoflurane concentration (0.35%) was lower ($P<0.05$) than in the women in placebo group (0.47%). At postanesthesia care unit, one patient in the fentanyl and placebo groups and two patients in the higher dexmedetomidine, had a heart rate of less than 45 beats/min, and a single dose of atropin, 0.4 mg, was administered i.v.

Discussion: Based on these preliminary results, it appears that dexmedetomidine reduces isoflurane dose requirements, in human. Moreover, our findings provide evidence that dexmedetomidine is able to inhibite potentially harmful sympathetic reflexes after laryngoscopy and intubation. An excessive bradycardia seemed not to be a problem in any phase of the study.

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Table I. Characteristics and the main results. (means±SE)

	Placebo	Fentanyl 2.0 µg/kg	Dexmedetomidine 0.3 µg/kg	Dexmedetomidine 0.6 µg/kg
Number of patients	24	24	24	24
Age	43±0.9	43±1.0	43±1.0	44±0.6
Weight (kg)	66±1.7	66±2.3	64±1.8	66±1.7
Height (cm)	164±1.1	163±1.2	165±1.3	163±1.3
Isoflurane concentration (%)	0.47±0.05	0.48±0.05	0.38±0.03	0.35±0.02*
Sedation scores	1.0±0.0	1.4±0.1**	1.2±0.1	1.5±0.1**
Max. syst. blood pressure (mmHg)	168±3.2	155±4.5 **	176±5.1	161±5*
Max. heart rate	106±3.3	101±4.5	106±4.5	87±3*

* = $P<0.05$, and ** = $P<0.01$ indicate differences compared with the placebo group.

TITLE: BREATHING PATTERNS AFTER THORACOTOMY

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INTRODUCTION:

Impaired diaphragmatic function is commonly observed following abdominal operations; systemic analgesics only partially reverse this abnormality.[1] The present study was undertaken to examine whether or not comparable changes occur in patients who have undergone thoracic surgery.

METHODS:

The subjects were 9 patients, mean age 61 ± 8 years, scheduled for elective thoracotomy. The protocol was approved by our IRB and informed consent was obtained. Preoperatively, measurements of tidal volume(V_t), respiratory rate (RR), rib cage motion/tidal volume ratio (RC/V_t), inspiratory duty cycle (Ti/T) and inspiratory flow (Vt/Ti) were performed using respiratory inductance plethysmography (Respigraph, NIMS, Miami, FL). Teflon-coated inductance coils of appropriate size were placed around the rib cage (RC) and abdomen (AB), with the upper edge of the rib cage band immediately below the axilla and the upper edge of the abdominal band at the umbilicus. The system was calibrated to the analog output of an Infomed spirometer.[2] The maximum difference accepted between the signals at the beginning of each measurement period was 10%.

Each measurement session was carried out first in the supine position and then 30° semi-erect. Data for each measurement were collected for 10 min. Postoperatively patients received I.M. morphine sulfate 0.05-0.10 mg/kg, prn. Adequacy of analgesia was judged prior to each study period. Pain was scored subjectively by the patient on a linear analog scale from 0 to 10 (0=no pain, 10=severe pain)[3]. Respiratory measurements were performed on postoperative day (POD) #1 and POD #3, 1-2 hrs after morphine administration. All results are expressed in mean ± S.E. Statistical comparisons were performed using Student's t-test for paired data. P<0.05 was regarded as significant.

RESULTS:

The table summarizes our results. Mean pain score during study periods was 2.5 with a range of 1 to 5. Comparing preoperative and postoperative respiratory function, we found no significant change in any of the parameters measured.

DISCUSSION:

Unlike the decreased abdominal motion seen after upper abdominal surgery,[1] thoracotomy patients receiving adequate systemic analgesia showed no change from preoperative values either in the supine or semi-erect positions. These findings are also different from thoracotomy patients who receive epidural fentanyl, where postoperative abdominal motion is also decreased.[4] Thus, we do not believe that the site of surgery is responsible for the difference between post-laparotomy and post-thoracotomy patients.

Adequacy of analgesia, however, does appear to be important in maintaining postoperative respiratory motion. When we attempted to study these patients prior to their receiving morphine, they were unable to cooperate. From this observation, we suspect that decreases in RC or abdominal motion after thoracotomy is abrogated by effective systemic analgesia.

We conclude that the effective use of narcotic analgesia after thoracotomy is associated with maintenance of a normal respiratory pattern; therefore, continuous forms of opioid analgesia such as IV infusions and/or patient-controlled analgesia may prove to be most effective in preserving respiratory function in the postoperative period.

	PREOP	POD#1	POD#3
SUPINE			
RC/Vt(%)	39.4±3.2	35.8±4.4	41.4±3.2
Vt(cc)	453±61	404±44	472±63
RR(bpm)	15.8±1.2	15.9±1.2	15.9±1.1
Ti\T	0.38±0.01	0.35±0.01	0.35±0.01
Vt\Ti(cc\s)	327±31	315±32	359±39
30°INCLINE	PREOP	POD#1	POD#3
RC/Vt(%)	40.9±3.4	43.3±4.6	44.0±2.5
Vt(cc)	443±48	432±48	447±53
RR(bpm)	16.7±1.1	15.2±1.1	15.3±0.9
Ti\T	0.37±0.01	0.33±0.02	0.35±0.02
Vt\Ti(cc\s)	338±32	349±39	345±33

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TITLE: EFFECT OF INCENTIVE SPIROMETRY ON BREATHING PATTERNS AFTER THORACOTOMY

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Introduction: Pulmonary complications remain the most frequent cause of postoperative morbidity after thoracotomy(T). Incentive spirometry (IS) is extensively used, although its superiority over other modalities of respiratory therapies has not been clearly demonstrated.[1] A recent study has shown that after cholecystectomy, the increase in tidal volume during IS is due to an increase in rib cage motion.2 We initiated the present study to examine the effects of IS on breathing patterns in post-thoracotomy patients receiving parenteral opioid analgesia. Specifically, we wished to examine whether, after chest surgery, IS causes an increase in ribcage motion similar to that described after cholecystectomy.

Methods: 9 consenting patients scheduled for elective T, mean age 61 yrs ± 7 SD, were studied with IRB approval. Tidal volume (V_t), respiratory rate (RR), inspiratory flow rate (V_t/Ti), inspiratory duty cycle(Ti/T), rib cage motion/tidal volume ratio (RC/V_t) were determined using respiratory inductance plethysmography (Respigraph, NIMS). Teflon-coated inductance coils of appropriate size were placed around the rib cage (RC) and abdomen (AB), with the upper edge of the rib cage band immediately below the axilla and the upper edge of the abdominal band at the umbilicus. The system was calibrated to the analog output of an Infomed spirometer.[3] The maximum difference accepted between the signals at the beginning of each measurement period was 10%. Postoperatively patients received morphine sulfate, 0.05-0.1 mg/kg IV or IM, p.r.n.

Adequacy of analgesia was judged prior to each study period. Pain was scored subjectively by the patient on a linear analog scale of 0 to 10 (0=no pain, 10=severe pain). Control measurements were performed at 30° upright on pre-op day 1 and repeated on post-op day 1 & 3 , at the following times: 1) before IS, 2) during IS, and 3) 5 min after IS. Statistical comparisons were per- formed using Student's t-test for paired data. P<.05 was regarded as significant.

Results: The table summarizes our results. IS provided immediate balanced recruitment of both RC and AB, and an increase in V_t/Ti. On POD#1, during IS, there was an overall reduction in V_t, whereas RC\Vt remained the same. On POD #3 there was a significant increase in the RC recruitment during IS. However, we could not identify any effect of IS that lasted as long as 5 minutes after termination of treatment.

Discussion: Immediately after surgery IS provided large increases in Vt by recruiting both AB and RC respiratory components, thereby assisting in expansion of all lung regions. On POD#3, however, there was a relative increase in the use of the RC component during IS. This increase may be due either to development of diaphragmatic dysfunction or, more likely, to a increased rib cage motion from a training effect induced by repeated IS encounters. The former is less likely, since an earlier study showed no significant diaphragmatic dysfunction after pulmonary resection.[4]

Another interesting observation was that Vt\Ti, a measure of respiratory drive, was unchanged throughout the study period. This is in agreement with observations made after cholecystectomy[2]. IS, however, appears to act differently following thoracotomy than after cholecystectcmy. In the latter, IS mainly increased RC on POD#1, whereas following thoracotomy we found a balanced increase in both RC and AB.

We conclude that the effects of IS are the result of an exaggeration of normal breathing. While this may help to prevent dependent atelectasis, it should be recognized that respiratory changes induced by IS are extremely transitory.

PRE OP	Pre IS	During IS	Post IS
RR(bpm)	16.1±1.1	16.2±1.2	15.6±1.3
Ti/T	0.37±0.01	0.43±0.03++	0.36±0.02
Vt(cc)	456±48	1535±169*	448±45
Vt/Ti(cc/s)	338±32	714±83 *	344±33
RC/Vt(%)	40.9±3.4	46.6±5.1	44.2±5.0

POST OP #1	Pre IS	During IS	Post IS
RR(bpm)	14.9±1.1	16.2±1.4	15.2±1.2
Ti/T	0.33±0.02	0.34±0.03	0.35±0.02
Vt(cc)	413±48	840±99 +	412±47
Vt/Ti(cc/s)	349±39	720±76 *	325±33
RC/Vt(%)	43.3±4.6	49.9±5.5	42.6±4.6

POST OP #3	Pre IS	During IS	Post IS
RR(bpm)	15.2±0.92	17.0±1.5	15.7±1.1
Ti/T	0.35±0.02	0.37±0.02	0.35±0.01
Vt(cc)	431±53	901±87 *	451±69
Vt/Ti(cc/s)	345±33	749±91 *	362±48
RC/Vt(%)	44.0±2.5	59.9±4.7**	42.7±2.6

** p < .003 vs Pre op   * p <.001 vs Pre IS
+ p < .002 vs Pre IS   ++ p <.001 vs Post op

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EFFECT OF NALTREXONE CHLORIDE UPON ARTERIAL PRESSURE DURING PREGNANCY IN RATS.

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Introduction: Opioid receptors were demonstrated by Perth & Snyder in 1973 (1). Since then, the endogenous opioid system (EOS) has been object of extensive investigation.

EOS plays an important role in the regulation of a variety of organic functions, including hemodynamic homeostasis (2).

This fact is illustrated by the improvement of cardiovascular function following administration of the opioid antagonists in several forms of shock (3). Indeed, EOS shares anatomical, physiological and pharmacological characteristics with cardiovascular centers.

Since EOS is also deeply affected by pregnancy (4), it may participate in the cardiovascular changes associated with this situation. We thus studied the effects on blood pressure of chronic EOS blockade during pregnancy in rats.

Methods: Wistar female rats were randomized in 4 groups: A (n=11) , B (n=10), C (n=10) and D (n=10). Animals from groups A and B were mated and became pregnant. Opioid antagonist naltrexone chloride (TREXAN, E.I. du Pont de Nemours & Co. Inc.), 5 mg/kg/b.i.d.was administered by gavage to the rats of group A from the 1st. to the 20th. day of pregnancy. The same treatment was given to the rats of group C. Groups B (pregnant) and D (non-pregnant) served as controls.

Body weight and tail arterial pressure (microphonic method) (5), were determined 2 days before and every third day during treatment (or pregnancy).

At the 20th. day all animals were sacrificed (in non-stressful conditions) . Complete necropsy was performed, including cranial contents, thoracic and abdominal organs. Before fixation in formol (10%) puppies were counted and weigthed. Hystologic preparation included hematoxilin-eosin and Weigert staining.

Statistical analysis consisted of one-way analysis of variance.

This protocol was approved by the University Ethical Comitee.

Results: Rats from the Group A (pregnancy + naltrexone) showed a significant ($p<0,001$) increase in arterial pressure (from 116.00 ±3.58 to 134.91 ±7.28 at the 20th. day). Untreated pregnant rats from the Group B showed a statistically significant ($p<0,001$) gradual decrease in arterial pressure (from 118.00 ±3.89 to 89.20 ±5.98 at the 20th day).

Arterial pressure remained unchanged in animals of the groups C and D.

No significant weight differences were noted between groups A and B (pregnant)or C and D (non-pregnant).

Puppies from group A were slightly but significantly ($p<0,05$) smaller than those from group B: 4.11 ±0.90 and 5.22 ±1.77, respectively.

No macroscopic changes were observed in any of the 4 groups studied. Under light microscopy, Grade 1 arteriolar benign nefrosclerosis (fibroelastic hyperplasia) was evident in all animals of group A (pregnancy + naltrexone). No such abnormalities were seen in animals of the other groups.

Discussion: Opioid antagonism by naltrexone not only prevents the progressive decrease in arterial pressure during pregnancy but rather, is associated with the development of significant hypertension and nefrosclerosis.

This effect was not observed in non pregnant control rats.

This fact strongly suggests that the endogenous opioid system participates in the regulation of blood pressure during pregnancy.

These results encourage further investigation on the role of the endogenous opioid system in the cardiovascular physiology and physiopathology of pregnancy.

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Title: CARDIOVASCULAR RESPONSES TO BODY TILT DURING SPINAL ANESTHESIA

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Introduction: Sinus bradycardia is one of well known cardiovascular responses to spinal anesthesia, which can potentially result in a sudden cardiac arrest(1, 2). The etiology has been attributed to either preganglionic block of cardiac accelerator fibers or a decrease in venous return to the heart, or to both (1). Reflex bradycardia or enhanced cardiac vagal tone have been suggested in the presence of decreased venous return during regional anesthesia (1, 3) Thus our study was undertaken to investigate the role of body tilt-induced variations of venous return in the control of heart rate and the other cardiovascular variables during low and high spinal anesthesia.

Methods: With the approval of our Institutional Human Studies Committee and after obtaining informed written consent, 40 ASA 1 patients undergoing spinal anesthesia for their surgical procedures were studied. No premedication was given. Heart rate(HR), arterial blood pressure, right atrial pressure(RAP), and cardiac output (CO) were measured by ECG,radial artery cannulation, catheterization in the right atrium via a basilic vein, and bioimpedance cardiography, respectively. Mean arterial pressure (MAP) was calculated. After a resting period of 30 min, control measurements were performed and followed by a 10-degree head-up (H-U) or head-down (H-D) body tilt. The hemodynamic data were obtained in each position when the RAP had stabilized. Spinal anesthesia was induced at the L3-4 interspace using 2.0 ml or 3.0 ml of 0.5 % tetracaine solution in 10 % dextrose to obtain the low(G-1,n=20) or high spinal anesthesia (G-2,n=20), respectively. When the superior analgesic level to pin-prick has fixed around the dermatome up to T-10 in G-1 or T-4 in G-2 at least 20 min after spinal injection, the second set of hemodynamic measurements was repeated both in the supine position and during body tilts. Thereafter 10 of 20 patients in each group received pentazocine 15 mg IV and diazepam 10 mg IV. When sedation and a stable hemodynamic period were obtained, the third set of hemodynamic measurements was performed. All values were expressed as mean ± SD. Statistical analyses of the results were performed by analysis of variance followed by Student's t-test with P<0.05 regarded as significant.

Results: G-1 and G-2 were similar in age(39 ± 11 vs. 38 ± 9) and sex (12M,8F vs. 10M,10F) except for the analgesic level in dermatome(T-10 ± 1.1 vs. T-4 ± 0.8). Although the induction of spinal anesthesia resulted in decreases in MAP and RAP (P<0.01), CO showed no significant changes (Table 1). After sedation CO decreased (P<0.01) and RAP increased (P<0.05 in G-2). Body tilt-induced changes in RAP (P<0.01) were similar before and after spinal anesthesia (Table 2). H-U was associated with a decrease in MAP and an increase in HR only after spinal anesthesia (P<0.05). H-D caused no significant changes in MAP but consistent decreases in HR either before or after spinal anesthesia (P<0.05). There were no significant differences in hemodynamic data between the two groups (Table 1,2).

Discussion: These data demonstrate that, even during high spinal anesthesia, arterial baroreflex mediated HR response remains functional in the face of an apparent decrease in venous return due to changes in body position, and that sedation does not impair this reflex HR response. Hence the changes in venous return are likely to have a minor role in the reflex control of HR during spinal anesthesia.

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Table 1. Baseline Hemodynamic Data(before body tilt)

	pre-spinal(n=20)	post-spinal(n=20)	after sedation(n=10)
HR (bpm)			
Low Spinal	67 ± 9	70 ± 11*	68 ± 9
High Spinal	72 ± 10	72 ± 12	65 ± 6
RAP (mmHg)			
Low Spinal	3.4 ± 0.8	2.2 ± 0.8**	2.5 ± 1.3
High Spinal	3.3 ± 0.6	2.0 ± 0.6**	3.1 ± 1.0^{+}
MAP (mmHg)			
Low Spinal	89 ± 10	81 ± 8**	82 ± 9*
High Spinal	89 ± 10	79 ± 10**	82 ± 9
CO (l·min^{-1})			
Low Spinal	4.5 ± 0.5	4.5 ± 0.5	4.0 ± 0.4**$^{++}$
High Spinal	4.7 ± 0.7	4.5 ± 0.7	3.8 ± 0.4**$^{++}$

See text for abbreviations. Values are mean ± SD.
*P<0.05, **P<0.01 compared with prespinal value.
$^{+}$P<0.05, $^{++}$P<0.01 compared with postspinal value.

Table 2. Changes in Cardiovascular Variables induced by Body Tilt

LOW SPINAL ANESTHESIA		pre-spinal(n=20)	post-spinal(n=20)	after sedation(n=10)
HR	H-U	0 ± 2	+6 ± 3**	+4 ± 2**
(bpm)	H-D	-1 ± 2*	-3 ± 2**	-1 ± 2*
RAP	H-U	-1.7 ± 0.5**	-1.7 ± 0.7**	-1.5 ± 0.6**
(mmHg)	H-D	+1.6 ± 0.5**	+1.3 ± 0.4**	+1.4 ± 0.7**
MAP	H-U	-0.8 ± 2.5	-2.1 ± 4.0*	-3.6 ± 5.5
(mmHg)	H-D	+0.8 ± 2.2	+1.5 ± 3.8	+1.2 ± 3.6
CO	H-U	-0.4 ± 0.3**	-0.3 ± 0.4**	-0.2 ± 0.2*
(l·min^{-1})	H-D	+0.4 ± 0.4**	+0.4 ± 0.4**	+0.2 ± 0.2*

HIGH SPINAL ANESTHESIA		pre-spinal(n=20)	post-spinal(n=20)	after sedation(n=10)
HR	H-U	0 ± 2	+6 ± 6**	+6 ± 4**
(bpm)	H-D	-2 ± 3**	-4 ± 3**	-2 ± 2*
RAP	H-U	-1.4 ± 0.6**	-1.7 ± 1.0**	-1.9 ± 0.8**
(mmHg)	H-D	+1.5 ± 0.6**	+1.7 ± 0.7**	+1.6 ± 0.8**
MAP	H-U	-1.0 ± 3.6	-4.7 ± 4.7**	-2.6 ± 4.3
(mmHg)	H-D	-0.7 ± 3.1	+1.6 ± 4.3	-0.3 ± 2.4
CO	H-U	-0.4 ± 0.3**	-0.5 ± 0.2**	-0.3 ± 0.2**
(l·min^{-1})	H-D	+0.3 ± 0.3**	+0.2 ± 0.2**	0.0 ± 0.3

Values are mean ± SD. *P<0.05, **P<0.01 compared between the values before and during body tilt.

Title: **ASSESSMENT OF RENAL BLOOD FLOW IN THE DOG WITH CONTRAST ULTRASOUND**

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Introduction Traditional monitoring techniques of renal function are inadequate for the early detection of renal dysfunction or the assessment of treatment efficacy. One would like to measure an index of renal function that predicts outcome and can be rapidly and easily determined. Renal blood flow (RBF) is known to influence glomerular filtration rate and tubular function and has been shown to predict viability in renal allografts. Although it is widely accepted that renal function is influenced by changes in RBF, the mechanisms regulating intrarenal blood flow distribution remain incompletely understood. The ability to easily assess regional RBF serially would enable one to answer many research and clinical questions about renal function during disease states and during pharmacologic interventions. We tested the hypothesis that contrast ultrasonography can be used to quantify renal blood flow.

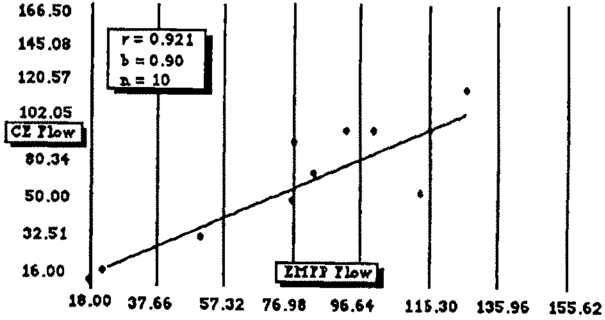
Methods After approval from our Animal Care Committee and with strict attention to NIH animal care guidelines, we induced anesthesia in six mongrel dogs with pentobarbital (15-25 mg/kg). An oral endotracheal tube was placed and the lungs were mechanically ventilated with a Harvard Ventilator (ET_{CO_2} 30-35 mmHg). The left carotid artery and right internal jugular vein were cannulated in order to record systemic blood pressures and to position a Swan-Ganz catheter. Temperature and pulmonary wedge pressure were maintained between 35-37 °C and 8-10 mmHg with a warming blanket and infusion of normal saline. Thermodilution cardiac output was measured in triplicate at end expiration, during control, and during experimentally altered conditions. A left flank incision allowed for exposure of the kidney and renal artery in order to secure an electromagnetic flow probe (Narco) around the left renal artery for control measurements of RBF. Ultrasound imaging of the kidney was performed with a 3.5 mHz modified ultrasound transducer secured over the outer surface of the left renal cortex. Baseline ultrasound image data were obtained by the injection of a bolus of sonicated albumin microbubbles through a femoral arterial catheter positioned in the thoracic aorta. As the bolus of contrast passed beneath the transducer, 25 consecutive images of the reflected ultrasound image of the kidney and aorta were captured in real time after conversion from radiofrequency to digital form. Data were then transferred to the RAM of a computer and loaded onto magnetic tape for off-line analysis. We used mechanical and pharmacological means to vary RBF in order to validate our method for calculating RBF with contrast ultrasonography.

Three developments enabled us to use contrast ultrasonography to quantitate renal blood flow: The availability of a stable contrast agent, a digital acquisition system, and a mathematical model for flow. A stable, small and non-toxic ultrasound contrast agent has been developed with the capability of capillary passage and, therefore, the ability to perfuse the kidney ultrastructure. Albunex® sonicated albumin microbubbles are smaller than red blood cells (RBC), and when injected into the vasculature, exhibit physiologic transit patterns that enable the microbubbles to serve as surrogate RBCs.[1] Secondly, the development of a digital ultrasound system enabled the direct access of ultrasound energy, including the entire dynamic range of the radiofrequency signal, without processing or distortion.[2,3] Finally, a mathematical model, specifically designed to quantitate analysis of tissue perfusion from contrast ultrasound techniques and based on classic dye dilution theory, has been developed and verified in a vitro model.[4]

Investigators blinded to the experimental protocol performed off-line analysis utilizing display of the digitally reconstructed 2-dimensional image of the kidney on a screen terminal. Two regions of interest were outlined. The first was a region of 100% blood volume (aorta) proximal to the kidney; the second was a region of the kidney (inner or outer cortex or corticomedullary junction) with variable blood volume. Mean pixel intensity for 25 consecutive images for each region of interest was determined, and time intensity curves for each region of interest were generated. Flow was calculated using the integrated area and mean transit times of the time intensity curves. RBF determined by ultrasound, vs. electromagnetic flow, determined by probe, were statistically analyzed using linear regression with $p < 0.05$ as the cutoff for statistical significance.

Results When we compared flow metered measurements to calculated flows, a correlation coefficient $r > 0.92$ ($p < 0.01$) was obtained for all animals (Fig. 1).

Fig. 1: Comparison of RBF Assessed by EMFP vs. CE



Discussion Many research and clinical questions could be answered if a method were available to serially measure RBF *in vivo*. This *in vivo* animal study provides a basis for the quantitative calculation of regional RBF by contrast ultrasound techniques. Ultimately, the ability to understand RBF in the animal laboratory may permit the dynamic assessment of perfusion in patients.

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Title: INCREASE OF ICP WITH SUCCINYLCHOLINE IN DOGS IS NOT PREVENTED BY CONTROL OF Pa_{CO_2} OR MEAN ARTERIAL PRESSURE

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Introduction. The role of Pa_{CO_2} and/or mean arterial blood pressure (MAP) in succinylcholine (S)-induced increase of intracranial pressure (ICP) is uncertain. One way to examine these issues would be to measure ICP, Pa_{CO_2} and MAP at frequent intervals following S and use statistical analysis to test the ICP-Pa_{CO_2} and ICP-MAP relationships. Another way would be to control Pa_{CO_2} or MAP following S and observe whether the increase of ICP was abolished. The present study was designed to utilize both of these approaches to examine the role of Pa_{CO_2} and MAP in S-induced increase of ICP in anesthetized dogs.

Methods. Following institutional approval, 31 dogs were anesthetized with halothane and surgically prepared for determination of ICP (via ventriculostomy), arterial blood gases, MAP and nasopharyngeal temperature. Dogs were randomly assigned to one of three groups. Group 1 (n=9) received S with no control of Pa_{CO_2} or MAP. Group 2 (n=12) received S with maintenance of expired CO_2 at pre-S values through ventilatory regulation by a servo controller and no control of MAP. Group 3 (n=10) received S with no control of Pa_{CO_2} and maintenance of MAP at pre-S values by intravenous infusion of trimethaphan with a syringe pump with doses based on previously reported studies. Trimethaphan was chosen to control MAP because it was reported not to exert a direct dilating action on cerebral vessels except at high concentrations. For all three groups the dose of S was 1.5 mg/kg, intravenously. Prior to administration of S CSF pressure, arterial blood-gas tensions, hemoglobin, MAP, heart rate and temperature were determined. At the time of administration of S (time 0) and at 1,2,3,4,5,7,10 and 15 min following S CSF pressure, Pa_{CO_2} and MAP were determined. Statistical comparisons within groups were made using repeated-measures and two way analysis of variance, and comparisons between groups were made using one way analysis of variance. The relationship between magnitude of increase of CSF pressure caused by S and change of Pa_{CO_2} and MAP also was determined by linear regression analysis and computation of the correlation coefficient. Values are tabulated as mean ± SD. The significance level was $p < 0.05$.

Results. S increased ICP (by 20-44%) in all three groups at 1-4 min (Table). Pa_{CO_2} and MAP increased in group 1, MAP (but not Pa_{CO_2}) increased in group 2 and Pa_{CO_2} (but not MAP) increased in group 3. Where Pa_{CO_2} or MAP was not controlled, Pa_{CO_2} increased at 3-10 min and MAP increased at 2-3 min. In all three groups the relationship between ICP and Pa_{CO_2} and/or MAP was not statistically significant.

Discussion. In the present studies the onset of ICP increase seen with S preceeded the increase of either Pa_{CO_2} (Groups 1 and 3) or MAP (Groups 1 and 2). ICP increase continued after MAP had returned to pre-S values (Groups 1 and 2). The period of increased ICP ended while Pa_{CO_2} still was increased (Groups 1 and 3). Moreover, the relationship between change of ICP and change of Pa_{CO_2} or MAP as assessed by analysis of variance and linear regression analysis was not statistically significant. These results suggest that the increase of ICP caused by S is not directly related to changes in Pa_{CO_2} or MAP. These results are consistent with a previously-reported proposal that S-induced increase of ICP is related to increase of muscle afferent activity and EEG activity, and do not support the hypothesis that S-induced increase of ICP is due to chiefly to changes in Pa_{CO_2} and MAP and can be abolished by preventing those changes.

Table. Values pre- and post- S, mean ± (SD)

Group 1 - no control of Pa_{CO_2} or MAP (n=9)	Time, min 0	 2	 7
ICP (cmH_2O)	8.9 (2.3)	12.8* (4.8)	10.2 (2.8)
Pa_{CO_2} (mmHg)	37.8 (3.5)	38.7 (5.9)	40.8* (3.5)
MAP (mmHg)	84 (7)	88* (8)	82 (9)
Group 2 - Pa_{CO_2} controlled (n=12)			
ICP (cmH_2O)	8.9 (3.0)	11.6* (3.9)	10.3 (3.3)
Pa_{CO_2} (mmHg)	37.0 (1.6)	38.1 (2.6)	38.1 (1.7)
MAP (mmHg)	82 (9)	86* (10)	80 (10)
Group 3 - MAP controlled (n=10)			
ICP (cmH_2O)	8.6 (2.2)	10.2* (2.1)	7.6 (2.5)
Pa_{CO_2} (mmHg)	36.7 (1.4)	36.8 (3.6)	38.0* (1.6)
MAP (mmHg)	85 (9)	82 (9)	81 (10)

* = Significant difference from values at time 0, $p < 0.05$

Title: CEREBROSPINAL FLUID DYNAMICS AND BRAIN TISSUE WATER AND ELECTROLYTES FOLLOWING HYPERTONIC SALINE IN RABBITS

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Introduction. Hypertonic saline has been proposed as an alternative treatment to mannitol, furosemide, urea or glucose as a means to lower intracranial pressure (ICP). Evidence favoring the use of hypertonic saline derives from reports that hypertonic saline minimized the increase of ICP and/or brain tissue water content in rabbits and dogs resuscitated from hemorrhagic hypotension, in rabbits with a cryogenic brain injury which were hemodiluted then resuscitated, in dogs resuscitated from endotoxic shock and in dogs with increased ICP secondary to glucose infusion. In all of these previous studies hypertonic saline was administered in a setting of either substantial hemodilution or an acute, severe cerebral lesion. Consequently, uncertainty exists regarding the effects of hypertonic saline on systemic variables (such as plasma and cerebrospinal fluid (CSF) osmolality (OSM) and electrolytes) under conditions more like usual clinical conditions. Additionally, there have been no studies under "normal" conditions to examine the effects of hypertonic saline on factors which regulate ICP, such as CSF volume and brain tissue volume. The present study was designed to examine the effects of hypertonic saline on systemic variables, CSF formation and reabsorption, and brain tissue water and electrolyte concentrations in anesthetized rabbits.

Methods. The protocol for these studies was reviewed and approved by the Animal Care Committee. Eighteen white New Zealand rabbits were surgically prepared for determination of CSF pressure (via ventricular cannula); plasma OSM, sodium and potassium concentrations; arterial blood gas tensions; mean arterial blood pressure; heart rate; hematocrit; and nasopharyngeal temperature. In group 1 (n=6) ventriculocisternal perfusion (VCP) was performed, no hypertonic saline was given and brain tissue water and electrolytes were determined at the end of the study. The purpose of this group was to determine the stability of systemic variables and establish "normal values" for brain tissue water and electrolytes in rabbits undergoing VCP. In group 2 (n=6) hypertonic saline was given, VCP was not performed and cisternal CSF was sampled every 40 min for determination of OSM and electrolytes. The purpose of this group was to determine the effect of hypertonic saline on CSF composition and on systemic variables (such as plasma OSM, etc.) in the absence of VCP. The changes in CSF composition observed in this group were used to alter the composition of mock CSF used for VCP in group 3. In group 3 (n=6) VCP was performed, hypertonic saline was given and the rate of CSF formation ($\dot{V}_f$), resistance to reabsorption of CSF (R_a) and brain tissue water and electrolytes were determined. With each dose of hypertonic saline the composition of the mock CSF infusion solution was altered according to the data obtained from group 2. The purpose of this group was to determine the effect of hypertonic saline on CSF dynamics, brain tissue composition and systemic variables (such as plasma OSM, etc.). Two doses of hypertonic saline were examined in both groups 2 and 3: a) 1.0 ml/min for 10 min followed by 1.5 ml/h and b) 1.0 ml/min for 30 min followed by 7.0 ml/h. Data were analyzed using one way and two way analysis of variance with a P value less than 0.05 considered significant.

Results. Both doses of hypertonic saline increased plasma and CSF OSM and R_a, and decreased $\dot{V}_f$ (Table). The larger dose of hypertonic saline decreased blood pH and bicarbonate concentration and increased plasma sodium concentration. At the end of the study, after infusion of both doses of hypertonic saline, brain tissue water content decreased and concentrations of sodium and potassium in brain tissue increased. Neither dose of hypertonic saline decreased CSF pressure.

Discussion. In this study reduction of brain water content (1.4%), when hypertonic saline raised plasma OSM by 7.2%, was similar to that previously reported with other hypertonic solutions: 1.8-2.9% when glucose was used to raise plasma OSM by 8%, 2.0-3.7% with mannitol, and 1.1% with lactated ringers. Decrease of $\dot{V}_f$ (30%), when hypertonic saline raised plasma OSM by 7.2%, was similar to that previously reported with other hypertonic solutions: 51% when mannitol was used to raise plasma OSM by 8%, and 17-57% when glucose was used to raise plasma OSM by 5.3-7.2%. Increase of R_a was most likely due to an increase in central venous pressure and increased cerebral vascular volume. When hypertonic saline is given by continuous infusion, decrease of $\dot{V}_f$ probably offsets increase of R_a causing little net change of CSF volume. Although brain tissue water decreased, CSF pressure did not decrease presumably because intracranial compliance was not compromised. The net OSM load produced by the two doses of hypertonic saline (12.3 mOsm/kg) produced an increase in plasma OSM (5.6%) that was similar to that previously reported with doses of mannitol, glucose and lactated ringer solutions with OSM loads of 37-46 mOsm/kg. The ratio of increase of CSF OSM to increase of plasma OSM with hypertonic saline (.71) also was greater than that previously reported with hypertonic glucose (.34). The cause for the greater potency of hypertonic saline is uncertain.

Table. Effects of hypertonic saline, mean ± SD

	Baseline	Dose 1	Dose 2
CSF pressure (cmH_2O)	7 ± 2	7 ± 2	7 ± 1
Plasma OSM (mOsm/kg)	270 ± 2	279 ± 4*	285 ± 5*
CSF OSM (mOsm/kg)	276 ± 6	282 ± 3*	287 ± 3*
$\dot{V}_f$ (microl/min)	10 ± 2	7 ± 2*	7 ± 2*
Brain tissue water (%)	80.1 ± 1.1	---	79.0 ± 0.4*

* = Significantly different from baseline, $p < 0.05$

TITLE: ANESTHETICS AND DILTIAZEM OR VERAPAMIL ON MECHANISMS FOR PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

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Introduction: AV node or AV node with accessory AV connection reentry accounts for 80% or more of cases of paroxysmal supraventricular tachycardia (PSVT).[1,2] SA node and atrial reentry are other possible mechanisms.[3] While iv diltiazem (DIL) or verapamil (VER) appear equally effective against clinical PSVT and have similar electrophysiologic properties[4,5], it has not been possible to test anesthetic effects against PSVT or determine their electrophysiological (EP) effects in patients. However, the actions of any of these drugs are of interest to anesthesiologists managing patients with known or suspected PSVT.

Except for SA node reentry[6], no reliable animal models for supraventricular (SV) reentry exist. However, it is generally appreciated that critical changes in cardiac conduction and refractoriness affect the likelihood of reentry, and DIL or VER effects on SV conduction and refractoriness do correlate with their effectiveness against clinical PSVT. We supposed that similar effects of these drugs or anesthetics on SV conduction and refractoriness in dogs might be useful in predicting anesthetic, or DIL or VER with anesthetics, effects against PSVT.

Methods: Conditioned mongrel dogs (N=26) were instrumented for chronic EP investigation.[7] Ten of these dogs underwent subsequent EP testing awake or anesthetized with end-tidal levels of enflurane (ENF), halothane (HAL) or isoflurane (ISO) equivalent to 1.2 or 1.6 MAC (dog). Sixteen dogs had similar testing with DIL or VER followed by testing with anesthetics. Awake dogs without drugs served as control, and dogs were tested once weekly in random order. EP testing included measurements of atrial and AV node refractory periods, AV node conduction time, Wenckebach point, and determination of the range of atrial premature intervals for sinus node reentry in dogs with such reentry (1/4 to 1/3 of dogs in each test group exhibited sinus node reentry in the control state). Standard clinical EP methods and definitions were used, and DIL and VER were administered iv to achieve levels (awake dogs) effective against PSVT. Statistical methods included overall ANOVA with Fisher's least sum difference test for pairwise comparisons. Significance was taken at $p<0.05$.

Results: Plasma levels of DIL or VER were approximately doubled by anesthetics, and in awake dogs of each anesthetic test group ranged from 66 to 79 and 127 to 145 ng/ml, respectively. There were no statistically significant effects of increased anesthetic level (any agent) on EP variables. Only ENF among the anesthetics increased AV node conduction time, with an average (1.2 and 1.6 MAC levels) 12% increase. Wenckebach point was unaffected by anesthetics. DIL and VER produced 27 and 46% increases in AV node conduction time, respectively. For Wenckebach point, increases were 36 and 52%, respectively. These same parameters were further increased by DIL or VER with any anesthetic, with increases over control values ranging form 67 to 121%. Some dogs with anesthetics and DIL or VER had type 1, 2° AV block or sinus arrest with escape rhythms, which was most common for ENF with VER. Anesthetics, DIL or VER had little effect alone, or in combination, on atrial effective and functional refractory periods. However, the atrial functional refractory period was increased (28 to 54% compared to control) by DIL with anesthetics. AV node functional refractoriness was increased by anesthetics (18 to 30%), DIL (19%) or VER (39%). With anesthetics, DIL produced an average (all agents) 88% increase in AV node functional refractoriness, and VER a 95% increase. Finally, anesthetics, DIL or VER, alone or in combination, abolished SA node reentry.

Discussion: Anesthetics, DIL and VER had similar effects on measured EP properties, suggesting that they might show similar effectiveness against clinical PSVT due to any of the four mechanisms for SV reentry. But, the latter would apply only to the extent that increased conduction times (AV node) and refractoriness (atrial, AV node) with DIL or VER is the mechanism for protection against clinical PSVT.[4,5] In combination, anesthetics and DIL or VER augmented the effects of each other against EP properties affecting SV reentry. This suggests that DIL or VER might be effective against PSVT in patients anesthetized with any of the potent inhalation anesthetics. However, any of this speculation as to effectiveness of DIL or VER against PSVT in anesthetized patients (potent inhalation agents only), or inhalation anesthetics against PSVT, must be viewed with caution due to possible species differences. It is quite unlikely, however, that EP testing to satisfy our speculation can be performed in man, at least with available technology.

If DIL and VER are both effective against PSVT in anesthetized patients, and PSVT did occur under these circumstances, DIL might be the preferred drug since it was associated with an apparent reduced risk of heart block or sinus arrest with any of the anesthetics. We note that DIL is currently undergoing clinical evaluation for parenteral (iv) use against PSVT[8] and atrial flutter or fibrillation.[9]

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TITLE: **THE CARDIAC EFFECTS OF PREOPERATIVE ORAL DIAZEPAM IN CHILDREN**

AUTHORS: SM Audenaert, M.D.,RL Lock, M.D., NW Pedigo, Ph.D., RE Akins, CRNA, and GL Johnson, M.D.
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Introduction. Orally administered diazepam is a frequently used preoperative anxiolytic, beneficial in easing the separation anxiety common in children. Despite an abundance of information on diazepam's pharmacodynamics, its cardiovascular effects as a pre-medication are incompletely defined in children. This investigation prospectively evaluated the effects of oral diazepam on echocardiographic measures of cardiac function.

Methods. Twenty (20) patients, ages 56 to 177 months and free of cardiac disease, were enrolled in the investigation with institutionally approved consent. During the day prior to elective surgery, consecutive cardiac cycles were evaluated following the technique of Meyer et al.[1] Evaluations were repeated three times over a 10-15 minute period and the last two sets used to define base-line cardiac function. The patient's activity levels were categorized as asleep, resting quietly, resting anxious, or agitated. On the day of surgery, patients received oral diazepam 0.3 mg/kg, up to a maximum dose of 15 mg. At an average of 70 minutes after administration, during peak plasma levels[2], 3 more sets of measurements were made and activity levels were again recorded. Data were analyzed for differences from base-line values using a repeated measures ANOVA.

Results. None of the patients were categorized as asleep or agitated either before or after diazepam. Quiet children did not differ from anxious ones in their pretreatment measures of heart rate (HR), ejection fraction (EF), or cardiac index (CI). Also, there were no significant changes in heart rate, ejection fraction, or cardiac index 40-120 minutes after diazepam for either group. (Table 1) There was a tendency towards an increase in heart rate for both quiet and anxious groups following diazepam administration. (Figure 1)

Table 1: Relative Effects of Preanesthetic Diazepam on Cardiovascular Parameters in Children

	HR	EF	CI
Quiet (N = 14)	109 ± 3	99 ± 2	109 ± 5
Anxious (N = 6)	104 ± 4	96 ± 4	100 ± 12

Data are mean ± SEM expressed as percent of pretreatment base-line values. Cardiovascular effects were assessed by echocardiographic techniques 40-120 minutes after diazepam administration.

Discussion. Oral diazepam is considered a cardiovascularly benign anxiolytic. This concept is largely based on information extrapolated from adults, where cardiac effects are reported to be minimal.[3] Using echocardiographic evidence we observed no significant changes in heart rate, ejection fraction or cardiac index in children receiving oral diazepam. These results suggest oral diazepam is without significant cardiovascular side effects and is an appropriate preoperative anxiolytic in children.

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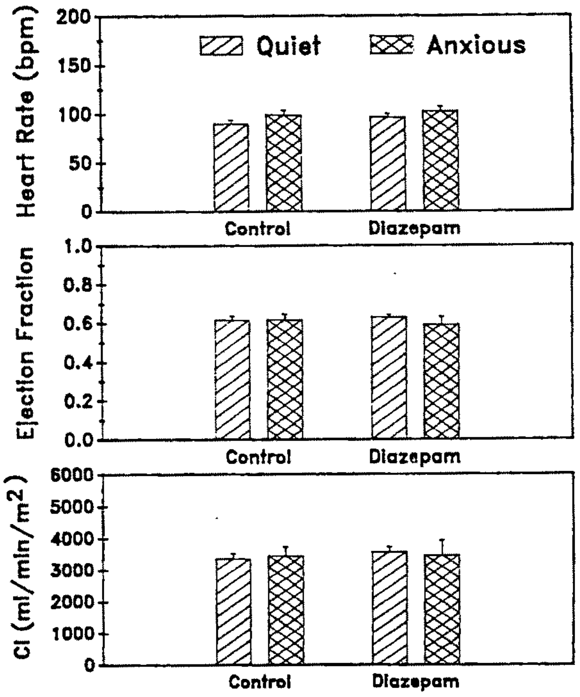
Figure 1: Cardiovascular Effects of Preanesthetic Diazepam in Quiet and Anxious Children



Title: THE RELATION BETWEEN TRANSCUTANEOUS AND ARTERIAL OXYGEN AT VARIOUS SITES IN HYPOXEMIC VOLUNTEERS

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Introduction. The ratio of transcutaneous oxygen tension (PtcO2) to arterial oxygen tension (PaO2) is known to be a function of both age and cardiac output (1). This ratio, called the "transcutaneous index" or TCI, has normal values of 1.1 for prematures, 1.0 for term neonates, 0.84 for children, 0.79 for young adults and 0.68 for the elderly. TCI has also been shown to decrease during hypoxemia (2). That is, when PaO2 decreased slowly in healthy volunteers, the PtcO2 actually fell at a faster rate. These measurements were all made with the probe on the chest heated to 44°C, and the lowest TCI value was 0.48 at a PaO2 of 38 mmHg. TCI has lower values on the extremities than on the torso, a fact that has been used to evaluate limb perfusion in the presence of vascular disease (3). It is not known whether the effect of hypoxemia upon TCI depends upon the location of the transcutaneous sensor. PtcO2 is frequently used to monitor neonates and infants in both the operating room and intensive care unit, and limited access to these patients often requires that the probes be placed on the extremities. The purpose of this study is to determine the effect of hypoxemia upon transcutaneous index for various probe locations on the torso and the extremities.

Methods. Twenty healthy adult volunteers participated in this study, which was approved by the human subjects review committee. Each subject was monitored with PtcO2 electrodes (Novametrix model 807) located on the chest, abdomen, medial thigh, medial calf, dorsum of foot and hand. All electrodes were heated to a temperature of 44°C. A 20 gauge radial artery cannula was inserted in the nondominant hand of each subject. After establishing baseline values for room air, subjects breathed mixtures of oxygen and nitrogen having FIO2 values as low as 0.10. Each FIO2 was maintained for at least five minutes, until steady state PtcO2 readings were obtained. At that time two arterial blood specimens were obtained for analysis by standard electrodes. The study was immediately terminated if a subject developed unpleasant symptoms or an arterial hemoglobin saturation of less than 72%.

Results. Transcutaneous index TCI is plotted versus PaO2 and probe site in Figure 1. Each point on this plot represents an average TCI over all subjects; standard deviations are indicated by error bars. There are several significant features of this figure. (1) The TCI at all probe sites decreases rapidly when PaO2 falls below 70 mmHg, and all sites except the hand show a similar slope. (2) For PaO2 > 70, the highest TCI (0.89) was found on the abdomen, followed by the chest, thigh, hand, calf, and foot. (3) At low PaO2, the hand and foot show the largest decreases in TCI, reaching values of 0.12 and 0.22 respectively. The differences noted are all statistically significant, $P < 0.01$.

Discussion. PtcO2 is a measure of oxygen delivery to tissue. As such, it is dependent upon local perfusion as well as arterial oxygenation. For this reason, transcutaneous index TCI is lower on the hands and feet than the torso even in healthy volunteers. TCI also falls during hypoxemia, and the traditional healthy adult value of 0.8 is valid only for normal to high PaO2. The largest decrease occurs on the hands and feet, where we obtained much lower TCI values than previously reported on the chest (2). However, on the calf and thigh the lowest TCI is no less than on the chest. PtcO2 monitoring on the thigh or calf should therefore follow PaO2 trends similarly to more central sites in healthy patients. The fact that TCI reaches very low values on the hands and feet during hypoxemia is consistent with the observation of peripheral cyanosis in hypoxemic patients.

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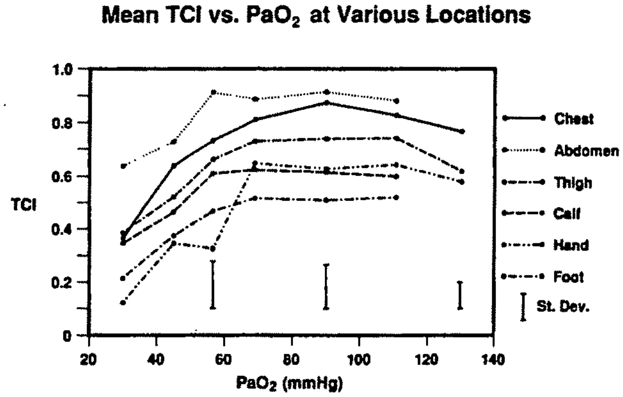
Figure 1. Mean values of TCI versus PaO2 at six probe sites.



TITLE: EFFECT OF ERYTHROMYCIN ON SUFENTANIL METABOLISM: DIFFERENCES FROM ALFENTANIL

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Introduction: Recently, the metabolism of alfentanil has been found to be prolonged when it is given after a course of erythromycin[1]. This has occasionally led to severe and long lasting post-operative respiratory depression. Sufentanil has a structure similar to alfentanil and undergoes similar oxidative metabolism in the liver. If erythromycin inhibits the metabolism of sufentanil in the same manner, it could also have an extended duration with the possibility of prolonged sedation and respiratory depression. On the other hand, if sufentanil is not affected by prior erythromycin administration, it can serve as a useful alternative to alfentanil in these cases. In order to determine which of these possibilities occurs, a controlled study of sufentanil pharmacokinetics was undertaken.

Methods: Six subjects who had previously volunteered for the study of erythromycin's effect on alfentanil gave written informed consent to participate in this Institutional Review Board approved study. Each subject was studied in three separate sessions spaced at least two weeks apart. Each study session was preceded by:

1. Nothing (control measurement),
2. A single dose of erythromycin (500 mg p.o. @ 6 A.M.), or
3. A seven day course of erythromycin (500 mg p.o. B.I.D.).

The order of these pretreatments was randomized. Subjects refrained from alcoholic beverages for a week and fasted from midnight on study days. Subjects were given naltrexone 50 mg p.o. @ 6:30 A.M. and naloxone 0.8 mg i.v. 5 minutes before the study to block the sedative and respiratory depressant effects of the narcotic. Sufentanil (3ug/kg) was infused i.v. over 5 minutes. Venous samples from a separate catheter in the opposite arm were collected at the following times after the start of infusion: 6, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420, 480, 540 and 600 minutes. Plasma was separated and frozen until the samples could be analyzed in duplicate by radioimmunoassay for sufentanil.

Plasma concentrations were analyzed by non-compartmental (area under the curve) methods. Each was fit to a sum of two exponentials to determine the elimination half life. This was used to extrapolate the tail of the concentration-time curve to determine clearance, volume of distribution and mean residence time. Parameters were subjected to analysis of variance (ANOVA) for repeated measures; $p<0.05$ was considered significant.

Results: Unlike alfentanil, the half-life and clearance of sufentanil were not significantly affected by erythromycin. The changes seen were generally small compared to the range of values in the group (Table 1). Furthermore, the actual plasma concentrations were not elevated in the studies after erythromycin when compared by ANOVA. This is seen in the curves of average plasma sufentanil concentration shown in fig.1.

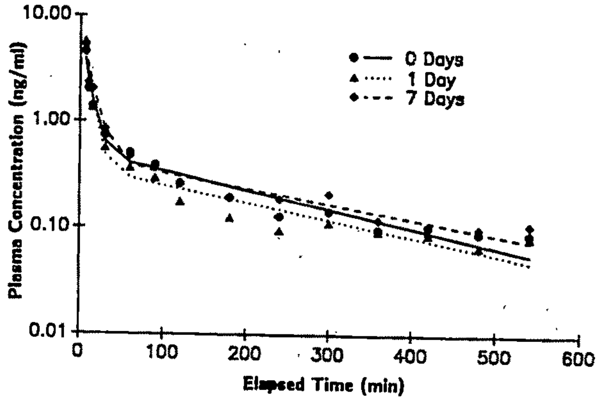

Figure 1. Average sufentanil levels for three different erythromycin pre-treatments.

Discussion: Erythromycin administration in the dose given here (1 gram daily for 7 days) does not markedly affect the elimination of sufentanil. Even if one were conservative and attributed the some of the individual changes measured in this study to an effect of erythromycin, these changes do not lead to plasma levels outside the norm for the group. This is in marked contrast to alfentanil whose levels were elevated under the same circumstances. One of the major differences between alfentanil and sufentanil is alfentanil's small volume of distribution (0.33±0.6 l/kg) which is more uniform from person to person. This leads to a more uniform elimination half life (84.0±8.2 min). Changes caused by drug induced reduction in clearance lead to a loss of predictability and increased duration of action. Sufentanil has a larger and more variable volume of distribution reflecting its increased lipid solubility. This leads to more intrinsic variability in the pharmacokinetic parameters. For sufentanil, there is no significant effect on the drug levels which in the end are responsible for drug action. Therefore even if erythromycin has a small effect that we were unable to prove because of high intrinsic variability, clinical consequences are unlikely. Sufentanil therefore is a reasonable choice of narcotic in patients who have had erythromycin and might have an abnormally prolonged course with alfentanil.

TABLE 1: Pharmacokinetic parameters for sufentanil after stated duration of erythromycin (Mean ± SD).

Parameter	0 Days	1 Day	7 Days
Clearance (ml/kg/min)	20 ±9	22 ±8	18 ±8
t 1/2(min)	169±89	203±105	231±54
VD_{area} (l/kg)	3.5±1.0	4.2±1.6	4.5±3.1
MRT (min)	190±73	205±113	235±72

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This study was supported in part by Janssen Pharmaceutica.

TITLE: EXCITATION-CONTRACTION COUPLING IN NEONATAL RABBIT MYOCARDIUM: EFFECTS OF HALOTHANE AND ISOFLURANE.

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Introduction. We evaluated the effects of isoflurane and halothane on action potential, peak generated force (F) and indices of sarcoplasmic reticulum (SR) function in right ventricular papillary muscles from neonatal rabbits using a sucrose gap myograph.

Neonatal myocardium is more sensitive to extracellular Ca^{++} and has a less well developed SR than adult myocardium. Two of the purported mechanisms of the depressant action of the volatile anesthetics are limitation of sarcolemmal (SL) Ca^{++} entry and/or SR Ca^{++} release. It hasbeen suggested that isoflurane may have a predominant effect on SL and halothane on both SL and SR Ca^{++}. If this is true, halothane might be relatively less depressant than isoflurane to neonatal myocardium compared to its effect in adult myocardium as any depression due to an effect on the SL would not be compounded by an additional major SR mediated effect. The effects of isoflurane in particular have not been well-studied in neonatal myocardium.

Methods. Muscles from 4-8 day old rabbits were studied with either halothane (18 muscles, 35 concentrations) or isoflurane (14 muscles, 19 concentrations) in the superfusate. Peak F, dF/dt for contraction and relaxation (dF/dt-C&R), action potential duration (APD), and height of the AP plateau at 50% APD (Ht$_{50}$) at a low stimulation rate (6/min) and following an acute increase to 30/min ("staircase"), an indicator of SR function, were recorded. Values during anesthetic exposure were compared to the mean of the preceding and following anesthetic free control periods. Regression formulae were calculated and values were normalized to the concentration of anesthetic causing 50% reduction in F for that anesthetic. (ED$_{50}$). This study was approved by the UCLA Chancellor's Animal Research Committee.

Results. Control F was similar in both groups (1.00± 0.12 and 1.11± 0.18 mN). The ED$_{50}$ was .25% for halothane and .54% for isoflurane (Figure 1). dF/dt-C and dF/dt-R both decreased with increasing anesthetic. APD was unchanged. Ht$_{50}$ decreased with increasing isoflurane ($P=.001$) and halothane ($P=.02$). Staircase F decreased with increasing anesthetic but there was no difference between halothane and isoflurane at the ED$_{50}$. The number of contractions to reach a new equilibrium staircase F was greater with anesthetic than without ($P=.01$ for halothane, $P<.01$ for isoflurane) but was not related to the concentration of anesthetic and the number of beats was similar for halothane and isoflurane.

Discussion. Both anesthetics were more depressant to neonatal myocardium than to adult myocardium. The ED$_{50}$ for halothane and isoflurane are significantly lower than that reported for adult rabbit papillary muscle[1] but are similar to those reported for halothane and isoflurane for neonatal rabbit atrial muscle[2]. The ratio of neonatal: reported adult ED$_{50}$ was similar for halothane (.42) and isoflurane (.39). Halothane and isoflurane both decreased Ht$_{50}$ suggesting an effect on membrane currents, such as the secondary inward or the repolarizing K^{+} currents, in neonatal rabbit myocardium. However any qualitative differences did not appear to cause significant decreases in F. Using these indices of SL and SR function, we could not demonstrate a preferential depressant effect of isoflurane in neonatal myocardium.

Supported in part by a Research Starter Grant from the Foundation for Anesthesia Education and Research (V.C.B.) and NIH grants HL01347 and HL 35783 (T.K.).

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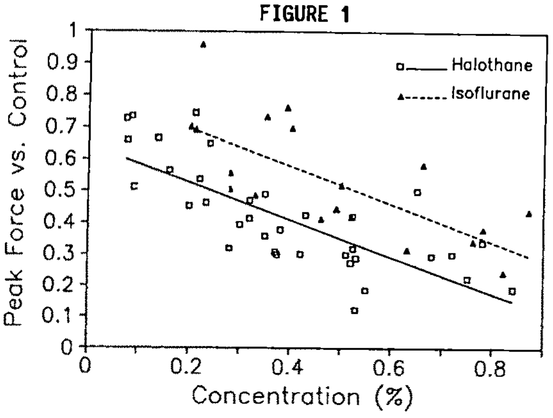
FIGURE 1



Title: HEMODYNAMIC EFFECTS OF ATRACURIUM AND VECURONIUM: A DOUBLE BLIND RANDOMIZED ASSESSMENT

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Introduction: Atracurium and vecuronium have stable hemodynamic profiles. However, hypotension and bradycardia have been reported to complicate the use of these agents. Elderly patients may have an altered response to these drugs due to their blunted autonomic responses.

A double blind randomized study was done comparing the hemodynamic effects of atracurium and vecuronium in young (age <40 yrs.) and old (age >60 yrs) patients.

Methods: Approval was obtained from our institutional ethics review committee, and after informed consent was obtained patients were stratified according to age and randomly assigned to receive either atracurium or vecuronium.

Anaesthetic: No patients received premedication. In the operating room patients received droperidol 10 μg/kg and diazepam 0.25 μg/kg IV. While breathing 100% O_2 patients received 0.5 to 1.0 μg/kg of sufentanil. At loss of respiration patients were ventilated with 60% N_2O and 40% O_2 via mask and given 0.5-1.5 mg/kg pentothal. The trachea was then intubated without the aid of muscle relaxation. Patients were then ventilated by volume cycle ventilator with tidal volume of 10 ml/kg at a rate of 12 breaths minute.

Muscle Relaxation: A Datex NMT 221 electromyograph was calibrated 3 times on each patient. When HR and BP was stable for 5 minutes, atracurium (0.5 mg/kg) or vecuronium (0.15 mg.kg) was injected over 1 minute.

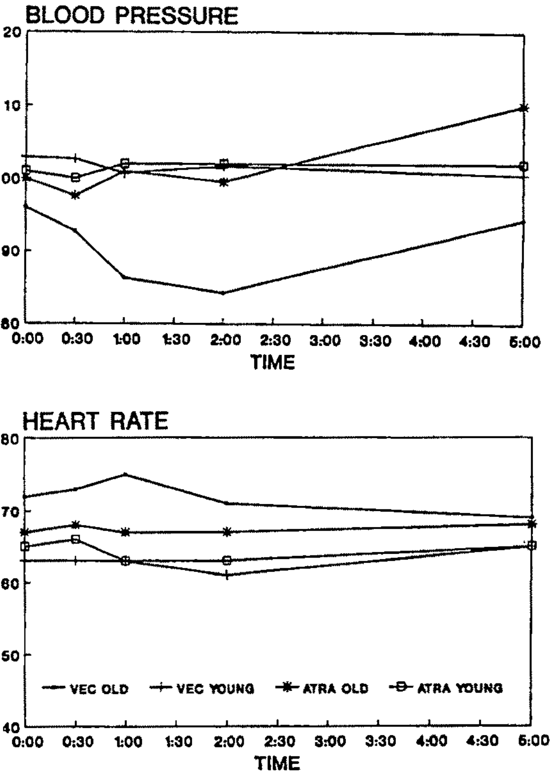
Hemodynamic Determinations: Heart rate and blood pressure were recorded every three minutes with a Dinamap (Model 221). At the time of injection the monitor was switched to STAT mode and recorded every 30 seconds for 5 minutes.

Statistics: Paired and non-paired t-test were used where appropriate. A P=0.05 was considered significant.

Results: The average age in young patients was 26.4 (vecuronium) and 28.2 (atracurium); in old patients it was 67.3 (vecuronium) and 67.6 (atracurium). There was a statistically significant decrease in systolic blood pressure with vecuronium in old patients. On average this was 10% of preinjection values. Heart rate was unaltered with both drugs and in young patients blood pressure was unchanged. The data are seen in Figure I.

Discussion: The decrease in blood pressure with vecuronium of 10 mmHg lasting less than 4 minutes is not likely to be clinically significant. Bolus doses of atracurium and vecuronium administered over 1 minute offer stable hemodynamic profiles.

Figure I



TITLE: **EPIDURAL INFUSION/PCA FOR PAIN CONTROL IN PEDIATRIC PATIENTS**

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Introduction. Epidural infusion/patient-controlled analgesia (EIPCA) has been employed at this institution to provide over 10,000 patient-days of pain relief after surgery or trauma. Based on this experience we have initiated EIPCA for postoperative/trauma pain relief in patients aged 6-18 years. This is a preliminary report of our experience.

Methods. This retrospective study has met the requirements of our Institutional Review Board. Twenty patients aged 6-18 years had eighteen gauge epidural catheters inserted for control of postoperative or trauma pain (Table 1). Whenever possible, a bolus of 0.02-0.03 mg/kg preservative-free morphine (PFMS) was given one hour before the end of surgery. In the PACU an epidural infusion of PFMS 0.02% was started at 5.0 mcg/kg/hr using a Bard PCA. In some individuals bupivacaine 0.625 or 1.25 mg/cc was added to the infusion. The PCA device was programmed to deliver 1.25 mcg/kg as a bolus dose with fifteen minute lockout. Unless dictated by operative procedure, ICU admission was not required and whenever surgically possible patients were discharged to wards. Standard orders are shown in illustration 1.

Results. There were no major complications associated with the use of EIPCA. All Patients received good or excellent pain relief as assessed by a verbal descriptive scale. No respiratory depression occurred. Side effects were mild and included pruritus, urinary retention and nausea.

Discussion. EIPCA is a safe and effective method of providing pain relief for pediatric patients after surgery or trauma. This technique combines the excellent pain relief provided by epidural narcotic/local anesthetic with the psychological benefits associated with autonomy and precise titration of analgesia.[1,2]

TABLE 1

Age	Procedure	Level	Side Effects	Duration (days)
6	Thoracotomy, lobectomy	T12,L1	P	7
9	Pubo-vaginal sling	L3-4		4
12-18	ACL (knee) repair (13 pts.)	L3-4	P(4),N(4) U(2)	2-3
11	Multiple rib fractures, thoracotomy	T11-12		9
17	Multiple rib fractures	T11-12	P	7
13	Anterior spinal fusion	L5-S1		6
13	Posterior spinal fusion	T11-12		5
13	Laparotomy, mass removal	L2-3		4

ILLUSTRATION 1

1. Please label chart and bedside "epidural ( ) narcotics ( ) local anesthetics".
2. Respiratory rate q. 1 hour for first 24 hr., then q. 2 hr. thereafter.
3. Temp. q. 4 hr. Notify pain resident for temp >102.0 degrees F.
4. Please give no parenteral narcotics, sedatives or systemic heparin; subq. heparin is allowable.
5. Please maintain I.V. access.
6. Morphine PF ______mg. bolus ______cc
   Epidural infusion: Please dilute the following to 50cc with PFNS
   Morphine PF　　Bupivacaine PF
   ( )5.0 mg(0.1 mg/cc)　　( )25mg(0.5 mg/cc)
   ( )10 mg(0.2 mg/cc)　　( )62.5 mg(1.25mg/cc)
   ( )______________　　( )______________
   Rate: __________ cc./hr.
   Via PCA machine: ______ PCA Bolus ______ cc.
   q.________ min.
   Via Travenol Infusor: __________
7. Change syringe, reservoir, or Travenol Infusor q. 24 hours.
8. Naloxone, 0.4 mg. amp and syringe taped to bedside.
9. Naloxone, 0.4 mg. minibag IV over 30 minutes for itching or urinary retention.
10. Naloxone, 0.4 mg. IV STAT for respiratory rate <8.
11. Ambulate as soon as possible.
12. Phenergan, 25 mg. IM q. 4-6 hrs. prn nausea.
13. Benadryl 25 mg. IM q. 4-6 hr. prn itching after 24 hours postop.
14. For any questions/problems related to pain management, page 221 or 985.

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TITLE: NEUROENDOCRINE CORRELATES OF LOWER ESOPHAGEAL CONTRACTILITY AND FRONTALIS MUSCLE ACTIVITY

AUTHORS: HL Bennett, Ph.D., DM Sullivan, B.S. and JE Savelle, B.A.
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INTRODUCTION. Assessing the adequacy of anesthesia in the unstable surgical patient is difficult. Monitoring lower esophagus contractility (LEC) and spontaneous frontalis EMG (FEMG) have both been proposed as a potential index of the adequacy of anesthesia (1,2). We evaluated LEC and FEMG responses during major operations where patients were at risk for inadequate anesthesia and compared them with hemodynamics and with plasma catecholamine levels sampled at five "stressor" points. We report a complex relationship between LEC and frontalis EMG activity reflecting different neuroendocrine stress activities.

METHODS. 48 major surgery or trauma patients, ASA III - IVE, who came to our operating rooms conscious and who were suitable for physiologic data recording were enrolled in the study. Informed consent was obtained with Human Subjects approval. Data were obtained every ten seconds throughout the operation from the spontaneous frontalis EMG (Datex ABM-100), and from pressure readings from the LEC pressure transducer (Lectron 302, American Antec). Blood pressure and heart rate readings were obtained every three minutes (Dinamap 1846, Critikon, Johnson & Johnson). Physiologic data were obtained from artifact free periods after induction of anesthesia and before emergence. Analogue LEC values were read directly from the Lectron 302 into the ABM-100 and written to a data disk. The FEMG values from the ABM-100 are normally displayed in a semi-logarithmic scale. These were converted to millivolts. Correlations between LEC and FEMG were then made for "stressor periods" when either LEC readings were above 15 mm Hg or FEMG voltage signals were greater than .75 mv.

Five intraoperative arterial blood samples were drawn from 22 patients for later HPLC analysis of serum catecholamine levels. The five catecholamine sample points included after intubation, after incision, during stimulating surgical manipulations, during closure, and just before reversal of anesthesia.

RESULTS. For 48 major operations there was an average of 128 "stressor periods" per case (sd.=148). The median correlation between LEC and FEMG activity for stressor periods over 48 cases was r= -.35 (p=.005). This implies an inverse relationship between frontalis EMG activity and LEC activity, possibly reflecting different or reciprocal stress responses between LEC and FEMG. Intermittent use of muscle relaxants sometimes made interpretation of the EMG data difficult.

Endocrine responses: There were 108 intraoperative blood samples from 22 patients. Table 1 provides the pertinent data. LEC and FEMG reflected different mechanisms of catecholamine activity. LEC was negatively associated with systolic and diastolic blood pressure increases while FEMG was positively associated with these traditional stress responses. LEC increases were positively associated with higher dopamine levels.

DISCUSSION. LEC appears to reflect dopaminergic autonomic activity. Significant negative correlations between LEC and frontalis EMG activity over 48 patients imply different stressor systems reflected in the two physiological measures. Catecholamine analysis supports this idea. Further work will examine in more depth these two systems of response to surgical stressors.

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1. Evans JM, Davies WL, Wise CC. Lower oesophageal contractility: a new monitor of anaesthesia. *Lancet*, 1984; May: 1151-1154.

2. Edmonds HL Jr, Couture LJ, Stolzy SL, Paloheimo M. Quantitative surface electromyography in anesthesia and critical care. *Int J Clin Monit and Compu.* 1986; 3: 135-145.

Table 1: Significant correlations (p<.05) among physiological and neuroendocrine variables from 108 intraoperative arterial samples in 22 patients.("-" = nonsignificant correlation; "xx"=correlation with same variable).

	NOREPI	DOPA	SYS	DIAS
SYS	.28	-	xx	.53
DIAS	.25	-.28	.53	xx
EMG volts	-	-	.14	.23
LEC mm Hg	-	.29	-.17	-.19

TITLE: TEST-DOSING FOR STELLATE GANGLION BLOCKADE IN ANESTHETIZED LAMBS

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Introduction

In awake adult humans, inadvertent injection of as little as 0.25 cc of local anesthetic into the vertebral artery (VA) during the performance of cervico-thoracic (stellate ganglion) sympathetic blockade (SGB) may cause immediate convulsions [1]. When SGB is required for infants and younger children, general anesthesia is often used, making detection of misplaced injection more difficult.

A newborn lamb model was developed to test the hypothesis that VA injection in animals spontaneously breathing halothane (H) 1 vol% would be detected by changes in clinical signs, including respiratory rate (RR), heart rate (HR), systolic and diastolic blood pressure (SBP,DBP), or pupillary diameter (PD).

Methods

Six 2-week old lambs were studied according to procedures approved by the Committee on Animal Investigation. They were anesthetized with H in oxygen (without other induction agents) and underwent tracheal intubation and placement of venous and arterial lines. A VA was cannulated under direct vision with care to avoid trauma to the vagus and phrenic nerves and the brachial plexus. Following cannulation, the inspired H concentration was maintained at 1% with spontaneous ventilation for 15 minutes, with end-tidal carbon dioxide ranging from 45-55 mm Hg. Lidocaine (L) 1% was injected into the VA catheter in increments as outlined in Table 1. HR, SBP, DBP, RR (using a Respitrace® impedance plethysmograph), and PD were recorded 30 seconds after each timed injection (T1-T7).

Results

Small test doses of L injected into the VA (T1-T2; analogous to administering increments of L 1%, 1.5-3 cc to adult humans) and full stellate block doses (T3-T4; analogous to L 1%, 5-18 cc for adult humans) produced no significant changes in RR and only modest decreases in BP (Table 1).

Very large doses of L injected into the VA (T5-T7) produced reductions in RR, brief apnea, and transient reductions in BP (Table 1); all parameters returned to baseline within 5-10 minutes. Increased PD was a variable finding with very large doses (T5-T7) only. No consistent changes in HR were observed at any dose, and no ictal movements were seen.

Discussion

VA injection of L in spontaneously breathing H-anesthetized lambs, in doses analogous to test doses or full SGB doses, does not produce reliable clinical warning signs. In particular, there was no detectable change in RR (or respiratory depth as gauged by impedance plethysmography or clinical observation) upon VA injection.

To the extent that infants resemble lambs, the above data imply that clinicians performing SGB for anesthetized infants (and perhaps older children) should be aware of the possibility of inadvertent intra-arterial injection despite the absence of changes in clinical parameters. Clinicians should be prepared to manage complications upon the patient's emergence from general anesthesia.

References

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Table 1 RR, SBP, and DBP Following VA Injection of L**

	L (mg/kg)	RR	%ΔRR†	SBP	DBP
Control	0	34±2	0	63±7	42±7
T_1	0.25	34±2	0	63±7	41±6
T_2	0.5	34±3	0	63±7	40±6
T_3	1	34±3	0	63±7	38±6
T_4	2.5	28±3	-17	57±5*	34±6*
T_5	5	19±3*	-45	52±4*	28±2*
T_6	5	16±5*	-54	45±5*	24±2*
T_7	5	18±9*	-48	47±6*	24±5*

† Percent change in RR (%ΔRR)
* Significant difference from control values: P<.05 (ANOVA with multiple means comparisons)
** Results expressed as mean±SE

P, 24555

TITLE: CONTINUOUS EPIDURAL BUPIVACAINE-FENTANYL INFUSIONS IN CHILDREN UNDERGOING UROLOGIC SURGERY

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Introduction

In adults, combined epidural infusion of opioids (O) and dilute concentrations of local anesthetics (LA) provides excellent postoperative analgesia with a high therapeutic ratio [1]. Experience with continuous epidural infusions of O/LA combinations in children has not been reported previously.

Methods

As the preliminary phase of an ongoing double-blind study approved by the Committee on Clinical Investigation, we reviewed the records of 18 children ages 6.5 ± 2.3 years (mean ± SD, range 3-11) having lower abdominal urologic surgery (ureteral reimplantation, megaureter repair, bladder extrophy repair). Following written informed parental consent, patients received a combined epidural-light general anesthetic. Epidural bupivacaine (B, 0.1-0.125%)-fentanyl (F, approx. 2 µg/cc) infusions were initiated post-operatively. B concentrations were decreased slightly (0.125->0.1%) if motor blockade became bothersome. No systemic opioids were administered. Nurses recorded respiratory rate (RR) q1h and blood pressure, heart rate, pain intensity (observational and self-report, at rest and with turning), and signs of sensory or motor blockade (Bromage scale [2]) q4h. Epidural infusions were adjusted to the minimum rate "SS" that produced near-complete pain relief (roughly equivalent to Objective Pain Scale [3] scores 0-2) both at rest and with turning.

Results

All epidural placements were technically successful, as judged by intra-operative course and sensory and/or motor blockade of both legs immediately post-operatively. Infusions were continued for 61±21 (mean±SD) hours post-operatively.

7 patients experienced little or no pain throughout their epidural course; 7 patients experienced episodes of mild pain with turning or with bladder spasms that responded to increased infusion rates. 3 patients were pain-free except for brief episodes (all less than 2 h in duration) of moderate pain which responded to rate increases. One 3-year old patient cried frequently (apparently from fear or anxiety over sensory and motor blockade) despite behavioral signs and verbal reports of adequate analgesia.

Initial and SS infusion rates required to produce analgesia were identical: 0.22 ± 0.06 cc/kg/hr. Dosing in mg/kg/hr (B) or µg/kg/hr (F) is shown in Table 1. The hourly dosing of B in mg/kg is less than that shown previously to result in safe plasma B levels in children via the epidural route [4].

No episodes of clinically significant somnolence, hypotension or hypoventilation occurred. Patients' minimum RR over the course of epidural blockade was 17.9 ± 2.3/min, and no RR less than 16/min was recorded. Emesis occurred for 5 patients (28%) on the operative night and for 3 patients (17%) thereafter. Pruritus was noted for 4 patients (22%).

Despite the dilute concentrations of bupivacaine used, partial motor blockade (Bromage score [2] 33%) was reported frequently (7 cases), though no patient had a Bromage score above 33%. 3 children appeared bothered by sensory or motor blockade, 2/3 responded well to reassurance and/or reduced infusion rates and concentrations.

Discussion

As with adults, combined epidural O/LA infusion may provide analgesia for children with a wide margin of safety. With combined infusions, the risk of either O-induced respiratory depression or LA toxicity may be diminished. Use of more dilute B concentrations may also diminish the dysphoria produced in some children due to dense sensory or motor blockade with higher B concentrations. With this initial background, a double-blind study is in progress more formally to assess efficacy and side-effects.

References

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[4] Desparmet, J., Meistelman, C., Barre, J. and Saint-Maurice, C., Continuous epidural infusion of bupivacaine for postoperative pain relief in children, Anesthesiology, 67 (1987) 108-110.

Table 1. Epidural Bupivacaine-Fentanyl Hourly Dosing*

	Bupivacaine (mg/kg/hr)	Fentanyl (µg/kg/hr)
IR**	0.26 ± 0.09 (0.15-0.49)	0.45 ± 0.16 (0.20-0.78)
SS	0.24 ± 0.08 (0.14-0.46)	0.48 ± 0.2 (0.16-0.90)

* mean ± SD; ranges in parentheses
** IR denotes initial rate, SS denotes steady state rates

Title: COMPARISON BETWEEN HEMODYNAMIC EFFECTS OF SEVOFLURANE AND ISOFLURANE IN CHRONICALLY INSTRUMENTED DOGS

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Introduction. Only limited information is available on the comparative hemodynamic effects of sevoflurane (Sevo) in chronically instrumented animal models. This study compared the hemodynamic effects of equipotent Sevo and Isoflurane (Iso) anesthesia.

Methods. The study was approved by the Baylor Animal Protocol Review Committee. As previously described[1], 22 healthy mongrel dogs were instrumented with a Tygon catheter in the abdominal aorta and left atrium, an electromagnetic flow probe around the pulmonary artery, and a miniature transducer in the left ventricle. At least 10 days after surgery, animals were studied. Dogs were randomly assigned to 2 groups, receiving either 1.2 and 2 MAC of Sevo (n=11), or Iso (n=11). After awake hemodynamic measurements, dogs were anesthetized by mask, intubated and ventilated with O_2-nitrogen-anesthetic mixture to maintain P_aO_2 and P_aCO_2 at awake levels. Sevo and Iso were maintained at constant end-tidal concentrations (infrared analyzer) for at least 15 min before measurements were started. Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and left ventricular maximum rate of tension (dP/dt) were continuously recorded. Data were analyzed by ANOVA. $P < 0.05$ was considered significant.

Results. Hemodynamic effects of Sevo and Iso are shown in table 1. At 1.2 MAC both Iso and Sevo produced hypotension, tachycardia, no change in CO, and a decrease in dP/dt. Although the increase from 1.2 MAC to 2 MAC resulted in a further decrease in MAP, HR remained unchanged. At 2 MAC, decreases were recorded in both CO and dP/dt. For the same decrease in MAP, the only intergroup difference was more pronounced tachycardia during Sevo anesthesia at 1.2 MAC.

Discussion. Except for HR, Sevo and Iso anesthesia produced similar hemodynamic changes. However, our results suggested that 1) the arterial baroreflex depression induced by both agents may be less marked during Sevo than Iso anesthesia, and 2) because HR was higher in the Sevo group than in the Iso group, and since no intergroup differences in afterload were observed, the depression of myocardial contractility may be more marked during Sevo anesthesia. Indeed, changes in dP/dt depend not only on myocardial contractility, but are also correlated with afterload and HR[2].

Table 1. Hemodynamic Effects of Sevoflurane (Sevo) and Isoflurane (Iso). Mean ± SEM.

		Awake	1.2 MAC	2 MAC
HR (beats/min)	Sevo	85±2	135±8*	131±6*
	Iso	82±4	108±8*°	113±8*
MAP (mmHg)	Sevo	96±3	75±3*	59±3*+
	Iso	99±5	75±3*	60±4*+
CO (1/min)	Sevo	1.9±0.1	2.1±0.2	1.6±0.2*+
	Iso	2.0±0.1	1.9±0.1	1.7±0.1*+
dP/dt (mmHg/s)	Sevo	3379±196	2043±175*	1297±109*+
	Iso	2915±165	1832±145*	1265±123*+
SVR mmHg/min/1	Sevo	50±3	39±4*	40±4*
	Iso	50±3	39±2*	36±2*

* when compared with Awake
+ when compared with 1.2 MAC
° when compared with Sevo

References.

1. Anesthesiology 1986; 64:560-567.
2. Am J Cardiol 1969; 23:515-526.

Title: HEXAMETHONIUM AND MIDAZOLAM TERMINATE CNS MEDIATED CARDIOVASCULAR TOXICITY OF BUPIVACAINE IN RABBITS

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Introduction. Large amounts of bupivacaine (BUPIV) given IV produce hypertension, tachycardia and dysrhythmias as the initial manifestation of cardiovascular toxicity. Recent reports have shown that this BUPIV-induced cardiovascular toxicity may be in part mediated by the central nervous system (CNS). Heavner reported hypertension, tachycardia and dysrhythmias after intracerebroventricular (ICV) administration of small (µg) amounts of BUPIV in cats (1). Bernards et al. reported that systemic premedication with midazolam (a CNS-acting gamma amino butyric acid (GABA) agonist) prevented hypertension and tachycardia and delayed dysrhythmias in pigs given large IV doses of BUPIV (2).

These studies suggested to us that BUPIV may produce cardiovascular toxicity in part by altering sympathetic nervous system (SNS) outflow from the CNS and that alteration of SNS activity is the result of BUPIV mediated interference with GABA function within the CNS. To test these hypotheses, a rabbit model was developed in which cardiac dysrhythmias and hypertension occurred with µg-amounts of BUPIV given ICV. We then examined the effect of ICV midazolam (a GABA agonist) and hexamethonium (a SNS ganglionic blocker) on the dysrhythmias and hypertension produced by ICV administration of BUPIV.

Methods. Following approval of the University of Washington Animal Care Committee, 9 rabbits were anesthetized with halothane (0.8%) in oxygen, intubated and mechanically ventilated. The right femoral artery was cannulated for blood pressure monitoring and blood sampling and an ear vein was cannulated for venous access. The left lateral cerebral ventricle and the cisterna magna were cannulated with 20 gauge needles. Ventriculocisternal perfusion (VCP) was established by perfusing mock CSF into the ventricular cannula and out through the cisternal cannula. BUPIV (0.5%) was administered by VCP at the rate of 0.0148 ml/min (74 µg/min) until dysrhythmias developed or 30 minutes elapsed. At the onset of dysrhythmias, 4 ml blood was withdrawn for later determination of BUPIV concentration. Ten minutes after onset of dysrhythmias, 0.1 ml (1 µg) midazolam was administered by VCP. When dysrhythmias recurred following administration of midazolam, hexamethonium (10 mg/kg) was administered IV. BP, ECG, EEG, end tidal CO_2 and CSF pressure were continuously monitored.

Results. Seven of 9 animals developed ventricular dysrhythmias in response to ICV administration of BUPIV; in 6 of these animals the dysrhythmias were sustained for > 10 min. The dose of BUPIV which produced dysrhythmias was 900 ± 700 µg (mean ± SD). BUPIV was undetectable in the plasma of 3 animals at the onset of dysrhythmias and averaged 0.2 ± 0.1 µg/ml in the remaining 4 animals. ICV midazolam was administered to all 6 animals which developed sustained dysrhythmias and terminated dysrhythmias in 4.4 ± 0.6 min in all 6. Dysrhythmias recurred in all 6 animals in 22.0 ± 0.9 min. Hexamethonium was administered to 5 of these 6 animals when dysrhythmias recurred and terminated the dysrhythmias in 14 ± 1 sec. Mean arterial pressure (MAP) increased significantly ($p < 0.05$) from baseline following ICV administration of BUPIV then returned to baseline values following ICV midazolam (Figure 1). When dysrhythmias recurred, MAP again increased significantly ($p < 0.05$) only to decrease significantly ($p < 0.05$) following administration of hexamethonium. Heart rate was not significantly different at any time.

Discussion. The occurrence of dysrhythmias and hypertension following ICV administration of BUPIV confirms earlier reports that entry of BUPIV into the CNS may play a role in the genesis of cardiovascular toxicity. The undetectable or negligible plasma BUPIV concentrations at the onset of dysrhythmias confirms that systemic absorption does not account for the dysrhythmias observed. The ability of hexamethonium to promptly terminate the dysrhythmias and hypertension associated with ICV BUPIV administration suggests that the SNS may be the final pathway mediating these effects. The ability of midazolam to terminate dysrhythmias and hypertension suggests that SNS hyperactivity may result from BUPIV mediated blockade of GABA neurons which are known to tonically inhibit SNS outflow from the CNS. That is, BUPIV may increase SNS outflow (resulting in hypertension and dysrhythmias) in much the same way that local anesthetics produce seizures - through preferential blockade of inhibitory neurons or synapses.

References.

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Change in MAP Following Bupivacaine, Midazolam and Recurrence of Dysrhythmias

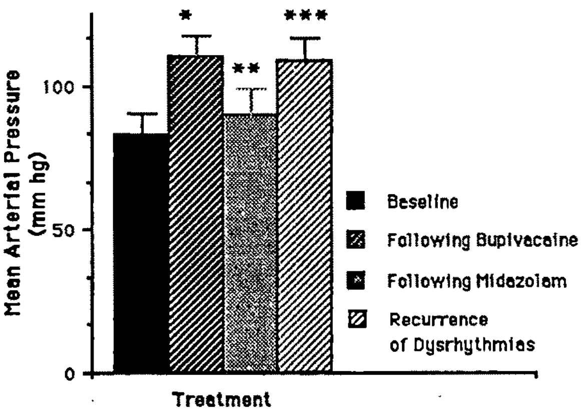

FIGURE 1: Data are mean ± SE. * $p < 0.05$ compared to baseline and midazolam. ** $p < 0.05$ compared to BUPIV and recurrence. *** $p < 0.05$ compared to midazolam and baseline.

Title: EFFECT OF DROPERIDOL ON PLATELET AGGREGATION AND ACUTE CORONARY THROMBUS FORMATION IN PIGS

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Introduction. We have previously shown that droperidol inhibits platelet aggregation and acute coronary thrombosis in dogs.[1] Whether or not this effect is specific to the dog or also occurs in other species is unknown. The purpose of this experiment was to determine if droperidol produces this potentially clinically important antithrombotic effect in pigs. In addition, we sought to determine if droperidol would also attenuate platelet aggregation when the intracoronary thrombotic process was augmented and accelerated by epinephrine infusion. (Epinephrine potentiates platelet aggregation at coronary stenoses.) A second aim was to determine if in vivo inhibition of coronary thrombus formation was reflected by changes in *ex vivo* measurements of platelet function obtained using aggregometry methods.

Methods. Following institutional approval, five pigs, 30-40 kg, were anesthetized with i.v. ketamine, fentanyl, and etomidate and their chests opened. A critical coronary stenosis was produced with a circumferential plastic constrictor around the proximal LAD coronary artery and both endothelial and extensive vessel wall damage induced. Platelet thrombosis and dislodgement of thrombus occurred, producing cyclical reductions in LAD coronary blood flow (CFR). Flow reductions were measured using an electromagnetic flow probe. Aortic, left ventricular, and pulmonary artery catheters were placed. Platelet aggregometer samples (method of Born) were drawn from fresh left atrial blood with 3.9% sodium citrate and the aggregation response to concentrations of ADP, collagen, and arachidonic acid (AA) were measured. Following a 30 min control period during spontaneous CFR, a 15 min epinephrine infusion (EPI, 0.25 $\mu g \cdot kg^{-1} min^{-1}$) was begun followed by droperidol infusion (0.8 $mg \cdot kg^{-1}$) over 15 min. Thirty minutes later EPI infusion was repeated and all parameters measured.

Results. Cyclical reductions in coronary blood flow produced by platelet thrombosis (CFR) occurred in all 5 animals. Epinephrine infusion exacerbated coronary thrombus formation, increasing CFR frequency. Droperidol infusion decreased CFR frequency (Table 1). Droperidol eliminated thrombus formation in 3 of 5 animals. Subsequent EPI infusion did not restore thrombus formation and CFR. *Ex vivo* collagen-induced platelet aggregation and ADP-induced aggregation was inhibited while arachidonate-induced platelet aggregation was not affected by droperidol (Table 2).

Discussion. The results indicate that droperidol effectively attenuates platelet aggregation and acute coronary thrombus formation in pigs. Platelet aggregation data suggests that droperidol is most effective in inhibiting collagen-induced platelet responses. Arachidonate-induced platelet aggregation was unchanged by droperidol, suggesting platelet cyclo-oxygenase inhibition is not responsible for the effect (aspirin, a cyclo-oxygenase inhibitor, does not prevent epinephrine induced thrombosis in this model). Inhibition of collagen induced platelet aggregation may be particularly important as rupture of atherosclerotic plaques in human coronary arteries exposes platelets to collagen, resulting in their activation and subsequent coronary thrombosis.

Table 1

Frequency of Cyclical Flow Reductions Caused by Platelet Aggregation and Coronary Thrombosis

Control	Stenosis and Vessel Wall Damage	Epi	Drop	Epi + Drop
0±0	0.15±.02	0.21±.01	0.08±.05	0.03±.05

n = 5
values are mean ± SEM

Table 2

Platelet Aggregation Studies

	ADP_{20}	ADP_{10}	ADP_5	C30†	C15§	AA7.7
	(light transmittance units)					
Control	18±4	24±3	18±2	42±6	19±6	65±4
Droperidol	21±5	19±3	13±3	21±8	7±3	63±5

† collagen 30%; § collagen 15%; AA arachidonate
n = 4
values are mean ± SEM

References.

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TITLE: PASSIVE OR ACTIVE INSPIRED GAS HUMIDIFICATION INCREASES THERMAL STEADY-STATE TEMPERATURES IN INFANTS

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Introduction. We tested the hypotheses that active and passive airway humidification minimizes intraoperative hypothermia in infants, but does not decrease the duration of postoperative recovery.

Methods. With approval of our Committee on Human Research and written consent, we anesthetized 30 infants (5-10 kg) undergoing peripheral surgery using isoflurane and nitrous oxide administered via a circle system. They were randomly assigned to *active* airway humidification and warming using an MR450 Servo® airway heater and humidifier set at 37°C (n = 10); *passive* airway humidification using the Humid-Vent® Mini heat and moisture exchanger placed between the Y-Piece of the circle system and the endotracheal tube (n = 10); or, no airway humidification and heating (*control*, n = 10). Airway humidity and rectal temperatures were recorded at 10-min intervals during the first 2 h of surgery. Fitness for discharge was based on standard criteria, including: 1) rectal temperature ≥ 36°C; 2) recovery period ≥ 30 min; 3) patient alert with stable vital signs; and, 4) no surgical problems. Patients were released from the recovery area by an anesthesiologist blinded to the method of airway humidification. Differences among groups were compared using one-way analysis of variance and Student-Newman-Keuls tests, and were considered statistically significant when $P < 0.05$. Results are presented as means ± standard deviations.

Results. Relative humidity of inspired respiratory gases was approximately 35% in the control group and approximately 90% in the group given active airway humidification. Initial inspired humidity in the passive humidification group was 45%, but increased to approximately 80% after 1 h of anesthesia The differences between groups were significant at all times, $P \leq 0.05$ (Fig. 1). Steady-state rectal temperatures (100-120 min after anesthetic induction) were 36.2 ± 0.7°C in patients given active humidification and heating, 35.7 ± 0.9°C in those receiving passive airway humidification, and 35.2 ± 0.4°C in the control patients ($P \leq 0.05$ between each group) (fig. 2). Recovery was rapid in all patients and duration did not correlate with rectal temperature changes or type of humidification (Control: 75±35 min, Passive: 84±27 min, Active: 78±25 min) (P = NS).

Discussion. We conclude that heat and moisture exchangers in infants are less effective than active heating and humidification, but significantly better than no humidification. Recovery was rapid, even in infants who became hypothermic during surgery.

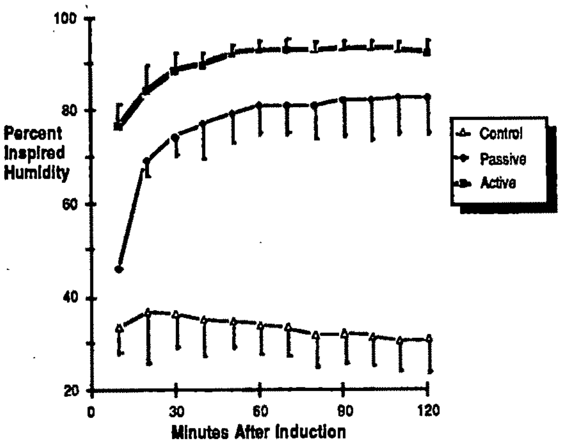

Fig. 1. Mean inspired relative humidity in 30 infants and children given active, passive, or no airway humidification. Humidity differed significantly among all groups at all times ($P < 0.05$).

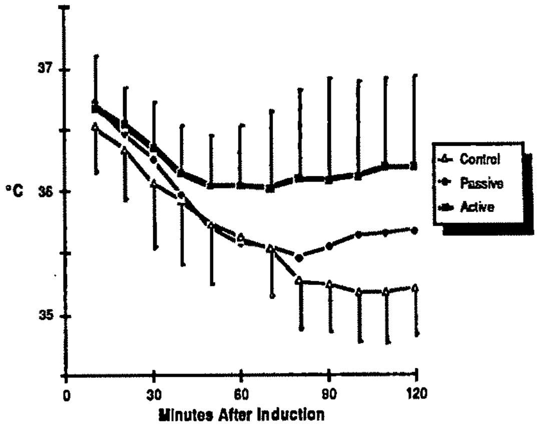

Fig. 2. Mean rectal temperatures decreased 0.5 ± 0.7°C in patients given active airway humidification, 1.0 ± 0.7°C in those given passive humidification, and 1.3 ± 0.6°C in the control group ($P < 0.05$, between each group). Standard deviations of the group given passive intraoperative humidification (omitted for clarity) were similar to those of the children given actively humidified respiratory gases.

Supported by NIH grant #R29 GM39723, Gibeck Respiration, Inc., and Mon-a-Therm, Inc.

TITLE: COGNITIVE RECOVERY AFTER PROLONGED ALFENTANIL INFUSION: MIDAZOLAM AND DIAZEPAM PREMEDICATION COMPARED

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Introduction: One advantage of alfentanil's short elimination half-life is a rapid return of cognitive function following brief anesthetics. After a prolonged alfentanil based infusion, however, drug accumulation may lead to delayed recovery. Since premedications can affect cognitive function, we compared recovery of cognitive functions in patients receiving an alfentanil based infusion lasting at least two hours and a preoperative dose of either midazolam, which a short half-life, or oral diazepam.

Methods: Twenty ASA I-III patients scheduled for elective lumbar discectomies gave informed written consents to participate in this Institutional Review Board approved study. Obese patients (>100 lbs over ideal weight), athletes and others with significantly altered pulmonary functions were excluded from enrolling. Preoperatively, Digit Substitution, Trieger Dot and Linear Analog Pain Scale were explained to patients and baseline values obtained. One half the patients (n=10) were then premedicated with 2-4 mg midazolam iv. The other patients (n=10) had received 10 mg diazepam po 30-60 min. prior to testing. Anesthesia was induced with alfentanil 75 ug/kg over 90 seconds and thiopental if required. Maintenance consisted of N_2O 60-70% with O_2, pancuronium, and alfentanil infusion (0.5-2.0 ug/kg/min.) as clinically indicated.

The infusion was discontinued 30 min. prior to the anticipated end of surgery; the time N_2O was discontinued was recorded as the end of surgery. Following surgery, patients' cognitive functions were tested every half hour until the patient required pain medication. Relationships were evaluated using analysis of variance for repeated measures ($p<0.05$ significant) with comparisons by the LSD test.

Results: There were no significant differences in demographics, total alfentanil dosage (average 18,027 ug) and times to extubation and immediate recovery between the two pretreatment groups. Length of surgeries were similar in each group, lasting an average 186.3 min.

Patients in both pretreatment groups performed significantly ($p<0.05$) worse than preoperatively on their first postoperative Digit Substitution Test. They showed significant ($p<0.05$) improvement on their second postoperative Digit Substitution Test, and, while still depressed by the third postoperative test (average 111 min. postop), were not significantly below baseline levels (Fig 1A). The preoperative baselines were significantly different between groups. The diazepam patients, who had already received their premedication, did significantly worse on preoperative tests than the unmedicated midazolam patients.

There were also no significant differences in recovery between the two groups on the Trieger Dot Test. Patients showed significantly (p<0.0.5) depressed performance on Trieger Dot Test compared to baseline at all postoperative times. The immediate postoperative test was the most depressed and patients showed significant improvement thereafter (Fig 1B).

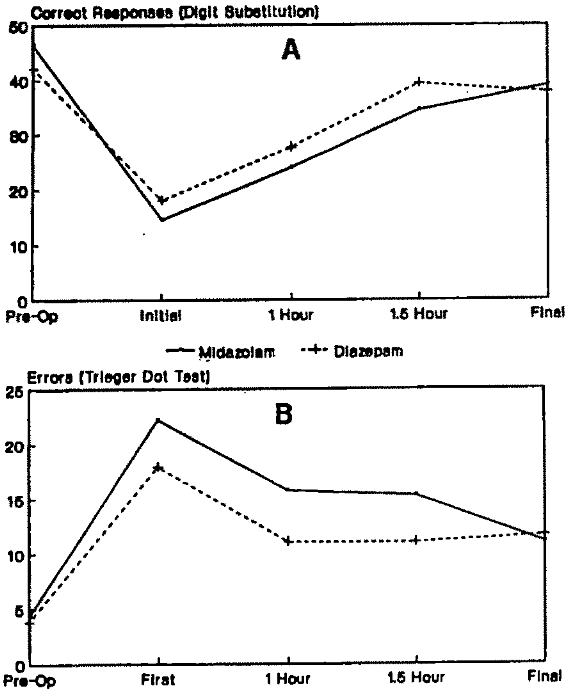

Figure 1 Digit Substitution (A) and Trieger Dot (B) Tests following prolonged alfentanil infusion for patients premedicated with diazepam and midazolam.

Preperative pain scores were not significantly different in the midazolam and diazepam groups. Pain rose significantly ($p<0.05$) from immediately postoperatively to the patients' last tested time.

Discussion: These results show that choosing between the two premedicants midazolam and diazepam does not alter recovery of cognitive functions nor the amount of postoperative pain after prolonged alfentanil based anesthesia. Following brief alfentanil anesthesia, patients can regain preoperative cognitive functions within 33-45 minutes (1,2). Our data shows however that despite alfentanil's short elimination half-life, return of cognitive functions to preoperative levels following a prolonged infusion will take over twice as long. The use of the shorter-acting premedicant midazolam instead of the somewhat longer-acting diazepam does not affect this recovery nor postoperative pain. The fact that premedicated patients who did not appear sedated performed worse on their baseline Digit Substitution Test indicates that our cognitive function tests are sensitive even to a small degree of sedation.

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Title: NOREPINEPHRINE CLEARANCE RATE AND RELEASE RATE IN MALIGNANT HYPERTHERMIC HUMANS

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Introduction. Malignant hyperthermia (MH) is a pharmacogenetic disease of swine and humans characterized by hypermetabolism and significantly increased activity of the sympathetic nervous system (SNS) following the administration of certain medications (1). Stimulation of the SNS can initiate an MH episode in susceptible swine and it is known that highly anxious MH susceptible patients are more likely to develop fulminant MH than are well-premedicated, calm patients. However, the role of the SNS in human MH is difficult to delineate. Compelling associations of sudden death and traumatic and emotional stress in MH susceptible families provide anecdotal evidence of increased SNS activity in human MH (2). Basal levels of plasma catecholamines are not elevated in MH susceptible humans but they responsed to decreased core temperature with higher NE levels than do control subjects, providing indirect evidence of altered SNS activity (3). Using a new technique (4) employing the infusion of tritiated NE, we were able to calculate the release rate (RR) and clearance rate (CL) of NE under resting conditions in normal and MH susceptible patients.

Methods. This study was approved by the Institutional Review Board and informed consent was obtained from each patient. Ten healthy controls and five MH susceptible patients were enrolled for study, with MH susceptibility diagnosed by a positive halothane-caffeine contracture test according to North American Malignant Hyperthermia Registry standards. At 0730 fasted patients were placed in the supine position and 20 gauge intravenous catheters were inserted in the right and left antecubital veins. The noninvasive blood pressure, electrocardiogram and temperature were monitored continuously. After a minimum of 30 minutes an infusion of tritiated NE [0.35 micrograms/meter squared/minute] was started in the dominant arm and continued for 90 minutes. Ten mililiter aliquots of blood were withdrawn from the dominant arm prior to the infusion and at 50, 70 and 90 minutes during the infusion. Blood samples were immediately centrifuged, and the plasma was then placed into tubes with 50 microliters of EGTA/glutathione solution and stored at - 70 Centigrade. NE was quantified following alumina extraction by liquid scintillation chromatography using a Packard 300C beta scintillation counter. Calculations of apparent RR of NE and of NE CL were made as follows:

$$RR = \frac{\text{3H-NE infusion rate (dpm/min)}}{\text{specific activity of plasma NE (dpm/pg)}}$$

$$CL = \frac{\text{3H-NE infusion rate (dpm/min)}}{\text{steady state plasma 3H-NE concentration (dpm/ml)}}$$

Results. Control subjects had a mean RR of 0.45 ± 0.10 micrograms/meter squared/minute and a mean CL of 2.28 ± 0.32 liters/minute. MH susceptible subjects had a mean RR of 0.44 ± 0.24 micrograms/meter squared/minute and a mean CL of 2.1 ± 0.78 liters per minute. CL and RR were not significantly different between groups ($P > 0.10$).

Discussion. Williams (5) has argued that the primary cause of MH is a defect in NE catabolism leading to the accumulation of NE in plasma. Our data obtained from resting patients do not support this contention. In documented MHS subjects and controls we failed to find any significant difference in the CL and RR of NE under basal conditions. The turnover of NE was the same in both groups. We cannot rule out an SNS abnormality which is expressed once an acute episode of MH is triggered. These studies cannot be conducted for two reasons. First, we cannot expose human subjects to triggering stimuli. Second, by definition Esler's method requires steady state conditions. Despite these limitations, our data suggests that the triggering site for MH is not in the SNS. These results are in agreement with previous studies (6) implying that abnormalities in SNS activity are not the primary cause of MH.

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TITLE: **THE EFFECTS OF HALOTHANE AND NOREPINEPHRINE ON DOMINANT AND SUBSIDIARY PACEMAKERS**

AUTHORS: **ZJ Bosnjak, PhD, S Polic, MD, PhD, LA Turner, MD, HK Schedewie, MD, PhD JL Atlee, MD and JP Kampine, MD, PhD**

AFFILIATION: **Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226**

Introduction: Sinus, atrial ectopic and AV junctional arrhythmias represent the most common rhythm disturbances in anesthetized patients.[1] Although the potent inhalational anesthetics about equally depress sinus node automaticity in the isolated SA node preparation,[2] the effects of anesthetics on subsidiary atrial pacemakers[3] have not been reported. The purpose of this study was to examine the effects of halothane and norepinephrine on the primary and subsidiary pacemakers using a perfused canine right atrial preparation.

Methods: Adult mongrel dogs were anesthetized with sodium pentobarbital. Following right thoracotomy the heart with at least 2 cm of superior vena cava was quickly excised and immersed in Krebs solution equilibrated with 97% O_2, 3% CO_2 mixture. The sinus node artery (SNA) was cannulated via the right coronary artery and the distribution of the flow was assessed by inspecting the distribution of 0.1 ml of dye injection. Ventricular tissue was removed and the right atrium preparation was transferred to an organ bath and pinned to the Sylgard floor with the epicardial side facing up. The SNA was perfused with Krebs solution at 36.0±0.5°C at a flow rate of approximately 4-5 ml/min. Four extracellular bipolar recording electrodes were used to record from the site of earliest activation (SEA) in relation to 3 sites of subsidiary pacemakers (as shown in the schematic drawing, Figure 1). The effects of halothane (1.1 mM) and norepinephrine (50 µg/L) on the SEA were examined separately and in combination in 13 right atrial preparations. The perfusate concentration of halothane was determined by gas chromatography.

Results: Halothane alone produced a slowing of the SA nodal rate from 75±6 to 65±5 bpm ($P<0.01$), while norepinephrine caused an increase in the pacemaker rate to 116±10 bpm ($P<0.01$). A combination of halothane and norepinephrine produced a rate of 102±13 bpm ($P<0.01$ vs control). As shown in the Figure 2 during the control, the SEA (electrode #1) precedes the activity recorded from the subsidiary pacemaker sites (2,3 and 4). Impulse propagation proceeds along the sulcus terminalis in the caudal direction. The SEA does not shift during either halothane or norepinephrine alone despite a slight shift in electrograms #2 and #3 in the presence of halothane. The last panel shows the combined effect of halothane and norepinephrine and a prominent shift in the SEA to the site of electrode #3. Shift in the pacemaker sites were seen in 7 out of 13 experiments and these effects were readily reversible.

Discussion: Our results suggest that halothane alters automaticity in dominant and subsidiary atrial pacemakers in a matter conducive to the formation of atrial rhythm disturbances. In the presence of catecholamines, this imbalance is enhanced and a pronounced shift in the pacemaker site could occur. Shifts in or wandering atrial pacemaker have previously been observed *in vivo* in dogs anesthetized with halothane and challenged with epinephrine.[4] Our hypothesis is that in the presence of norepinephrine, halothane depresses the automaticity of primary pacemaker more than the automaticity of subsidiary pacemakers. The cellular basis for this differential effect remains to be elucidated.

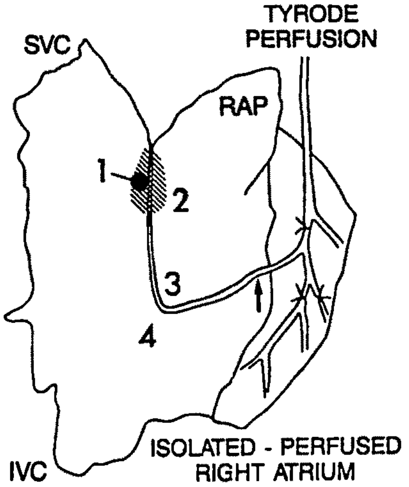

Figure 1. Perfused right atrial preparation of the dog with four electrode sites. The perfusion cannula is introduced into the sinoatrial artery up to the point indicated by the arrow. The site of earliest activation is in the shaded area (#1). Three stationary extracellular electrodes are positioned along the sulcus terminalis at sites 2, 3 and 4. SVC = superior vena cava; IVC = inferior vena cava; RAP = right atrial appendage.

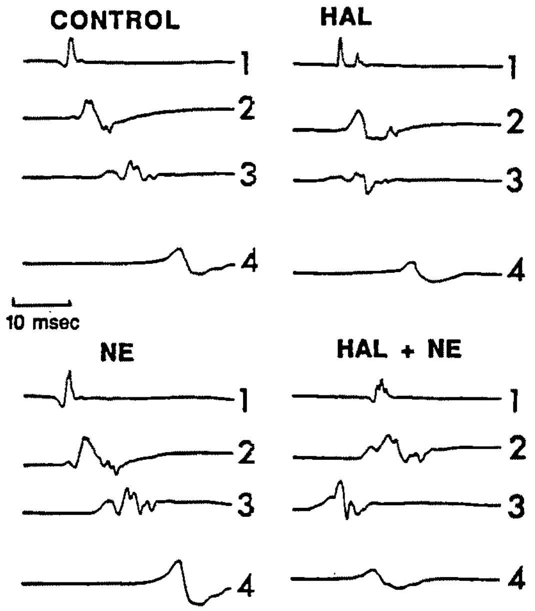

Figure 2. The site of earliest activation (electrogram #1) precedes the activity recorded from reference electrograms, and activation proceeds along the sulcus terminalis in the caudal direction (2 to 3 to 4, control). In the presence of halothane there is a slight shift in the electrograms #2 and #3 with earliest activation in the SA nodal region. The last panel shows the combined effects of halothane and norepinephrine and a prominent shift in the site of earliest activation to the site of electrode #3.

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TITLE: DIRECT SPINAL CORD EVOKED POTENTIALS DURING SPINAL ANESTHESIA

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AFFILIATION: Departments of Anesthesiology and Neurosurgery, University of Arizona College of Medicine, Tucson, Arizona 85724

INTRODUCTION: Although the molecular mechanism of action of spinal anesthetics is relatively well-understood, the precise site of action of local anesthetics on the neuraxis remains speculative. Urban (1) proposed that spinal anesthetics act on the spinal cord as well as on spinal rootlets, a hypothesis consistent with an earlier observation that local anesthetics penetrate the cord, at least in the dog (2). However, attempts to substantiate this hypothesis, by studying recession of subarachnoid anesthesia in humans, have been inconclusive (3).

We had the opportunity to observe the effects of lidocaine spinal anesthesia on cord conduction during direct cord stimulation and recording of somatosensory evoked potentials (SSEPs), while surgically implanting epidural spinal cord stimulators (SCS) for treatment of chronic pain. Spinal anesthesia has not generally been employed for placement of SCS electrodes due to the belief that it will abolish stimulation-induced paresthesias, which when described by the patient are used to refine the position of the electrode. We report the successful placement of SCS electrodes under spinal anesthesia, without obliteration of referred paresthesias or scalp-recorded evoked potentials (EPs), elicited by direct spinal cord stimulation during SCS implantation.

METHODS: Five patients, four men and one woman, mean age 53 years (range 27 to 79 years) were treated. All were admitted to the hospital for elective placement of SCS, for treatment of chronic pain of the lower back and legs. Written institutional informed consent was obtained from all patients. Operations were carried out in the prone position under C-arm fluoroscopy after placement of spinal anesthesia, which was indicated for tunneling of the electrode leads and placement of the SCS generator. Lidocaine spinal anesthetics (in 7.5% dextrose) were administered in the sitting (4 patients) or lateral decubitus position (1 patient). Four patients received 100 mg of lidocaine and one received 90 mg; epinephrine was used to prolong the duration of the spinal in 2 of the 5 cases. Sensory levels were determined by pinprick and cold-spray. Anesthetic dosages were chosen to provide a sufficient level of anesthesia (>T10) for about 1.5 hours, to allow for patient positioning and subsequent implantation of the SCS. SSEPs and direct spinal cord stimulation and recording are routinely employed at out institution for various neurosurgical and orthopedic procedures. In this series of patients, a Nicolet Pathfinder was used in conjunction with a Neuromed generator for Neuromed Octrode epidural lead stimulation and recording. EPs were recorded at the scalp during tibial nerve or direct spinal cord stimulation. Stimulation frequencies varied from 2 Hz. to 20 Hz. Current required for threshold stimulation was varied, to a maximum of 20 mA.

RESULTS: Spinal anesthesia resulted in satisfactory surgical anesthesia with complete sensory and motor blockade of the lower extremities and sensory levels extending to the upper thoracic dermatomes (T7 to T1). SCS epidural electrodes were inserted percutaneously using a specially designed Tuohy needle, and positioned to approximately T10 under fluoroscopic guidance. This was usually accomplished within 30 to 45 minutes. The epidural leads were then connected to a hand-held Neuromed generator for trial stimulation. In four patients (sensory levels of T7 to T1), stimulator-induced paresthesias were felt in the lower back and legs. In the fifth patient, who had a sensory level of T3, paresthesias were obtained using the Nicolet as a generator (10 -11 mA of stimulating current, which exceeded the output of the Neuromed generator). Concurrently, direct cord (T10) to scalp EPs, with consistent and reproducible wave forms, were obtained in all patients. However, dampening of wave forms was noted in some patients, and higher stimulating currents were required to produce identifiable evoked potentials. Although amplitudes of waves were decreased, latencies were not altered. As sensory levels began to recede, less current was required to obtain satisfactory EPs. Although spinal anesthesia completely obliterated lower extremity SSEPs, all patients felt referred paresthesias to the lower back and legs by direct cord stimulation, at currents that produced scalp-recorded EPs. Thus, EPs were objective verification of patients' reports of paresthesias. Paresthesias obtained during trial stimulation with the Neuromed generator during lead placement under spinal anesthesia were identical to those reported by patients postoperatively. Except for the use of small amounts of midazolam (2 to 4 mg) or fentanyl (50 to 100 mcg), spinal anesthesia obviated the need for analgesics or sedation during the procedure. All patients have obtained excellent initial pain control with SCS.

DISCUSSION: In all cases, trial paresthesias were discerned by the patients in the presence of spinal anesthesia extending three to nine dermatomes above the level of cord stimulation. Although the predominant site of action of local anesthetics appears to be at spinal rootlets, since lower extremity SSEPs were completely obliterated, there may also be a direct effect on the cord itself, since a blunting of direct cord to scalp EPs was observed at higher levels of spinal anesthesia.

The option of implanting SCS systems under spinal anesthesia has proven useful, based on improved patient comfort and cooperation during the surgical procedure, and may improve outcome by increasing the accuracy of lead placement. The ability of patients to accurately describe the distribution of referred paresthesias, under spinal anesthesia, greatly facilitated lead positioning. The use of spinal anesthesia may reduce the need for sedation, amnestics and injection of local anesthetics, usually required for subcutaneous tunneling during lead and generator placement. Avoidance of high levels of spinal anesthesia should allow use of the Neuromed generator for eliciting paresthesias in most patients. Use of continuous spinal anesthesia may facilitate obtaining accurate, predictable levels of spinal anesthesia, without blunting or obscuring trial paresthesias.

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Title: CARBON DIOXIDE REBREATHING DURING CATARACT SURGERY
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INTRODUCTION: Ophthalmologic surgery is commonly performed on awake patients utilizing retrobulbar anesthesia.[1] Concern about the possibility of carbon dioxide (CO_2) rebreathing produced by application of a plastic drape during cataract surgery has been longstanding.[2-5] Despite the fact that the majority of these papers have failed to document the presence of significant amounts of inspired CO_2 (ICO_2),[2-4] devices have been proposed to prevent this phenomenon.[2-4] The current study evaluated inspired and end-tidal CO_2 ($ETCO_2$) on patients undergoing elective cataract surgery. A modified nasal cannula with documented accuracy[6] for sampling $ETCO_2$ during simultaneous insufflation of oxygen (O_2) was used in this study.

METHODS: Following approval of our institutional review board approval, 25 consecutive unpremedicated patients scheduled for cataract surgery under monitored anesthesia care were studied. Each patient was monitored with EKG, BP, pulse oximetry and a modified nasal cannula which permitted insufflation of O_2 into one nostril and sampling of exhaled gases from the other.

Following application of all monitors, each patient received methohexital as necessary for a retrobulbar block. No other medications were administered. The surgical field was prepped and a plastic sheet (Steri-Drape 1030) was applied. Time of application was recorded. At the conclusion of the operation the drape was removed, time was recorded, and monitoring was discontinued.

Values for ICO_2, $ETCO_2$, RR, and capnometer waveforms were analyzed for the period prior to application of the drape (Control) and during the presence of the drape (Drape). Confidence intervals were calculated for ICO_2 in both periods and for $ETCO_2$ and RR during Drape expressed as per cent Control. Values for ICO_2 following removal of the plastic drape were noted.

RESULTS: 25 patients (age = 74 ± 9.0 yrs) were studied. All patients were awake and alert prior to application of the drape. Pulse, BP, and EKG remained within acceptable limits, considering initial values, throughout the study. S_aO_2 remained >.90 during O_2 insufflation.

Data are presented in Table One. Capnometer waveforms during Control manifested a normal pattern. During Drape, however, waveforms failed to return to baseline, indicating CO_2 rebreathing. No other abnormalities were noted in the shape of capnometer waveform. Waveforms returned to normal following removal of the drape. Immediately after application of the drape, ICO_2 was detected in every patient and remained present throughout Drape. Removal of the sheet was associated with an immediate disappearance of ICO_2 in every patient.

$ETCO_2$ (expressed as per cent of control) increased during Drape (1% confidence intervals = 102 to 113%). Respiratory rate remained unchanged (5% confidence interval = 92 to 104%). ICO_2 > 1% occurred for several minutes in 5 (20%) of patients. No patient complained of dyspnea or any other respiratory symptoms.

TABLE ONE (Mean ± standard deviation)

	ICO_2(%)	$ETCO_2$(%)	RR(min^{-1})
Control	0.00±0.00	4.59±0.68	16±3.5
Drape	0.49±0.22*	4.91±0.60	16±2.1

* $p < .001$ versus Control

DISCUSSION: This study demonstrates that application of a drape during ophthalmologic surgery may produce an increase in $ETCO_2$ as a consequence of CO_2 rebreathing. ICO_2 was demonstrated even before application of the drape in one study reporting on the smothering effect of draping during eye surgery.[5] The accuracy of the sampling technique used in that study has been questioned.[7] CO_2 rebreathing produces an increase in either alveolar ventilation ($\dot{V}_A$) or arterial CO_2 ($PaCO_2$). The increased work of breathing imposed by an increase in $\dot{V}_A$ may be deleterious in certain patients. Elderly patients with lung disease may be unable to increase $\dot{V}_A$ as needed to maintain a constant arterial PCO_2. The hazards of hypercarbia are well described. Increases in alveolar PCO_2 (as demonstrated by increased $ETCO_2$) are associated with decreases in alveolar PO_2. Supplemental O_2 is necessary to prevent consequent decreases in arterial PO_2.

The potential for CO_2 rebreathing during ophthalmologic surgery should be appreciated. Care should be taken to minimize the magnitude and consequences of this problem.

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Title: AUDITORY STEADY-STATE EVOKED RESPONSE DURING SUFENTANIL ANESTHESIA

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Introduction: High-dose opioid anesthesia is popular because of its minimal hemodynamic effects. However, there are reservations as to whether opioids reliably produce unconsciousness (1).
The 40 Hz auditory steady-state response (ASSR) is a sustained, sinusoidal evoked potential which is reduced in amplitude during low levels of arousal (2,3). We have recorded the ASSR during high-dose sufentanil anesthesia.
Methods: After institutional approval and informed consent, 8 patients undergoing elective aortocoronary bypass were studied. Patients were premedicated with lorazepam 0.04-0.06 mg/kg PO 90 minutes preoperatively. Anesthesia was induced with sufentanil 5 ug/kg. Incremental sufentanil 1-5 ug/kg was administered prior to skin incision, sternotomy and cardiopulmonary bypass (CPB). Rises in blood pressure or heart rate were treated with vasodilators and beta-blockers respectively. Recordings were performed before induction (BASE), during early (IND-A) and late induction (IND-B), after endotracheal intubation (VENT), during surgery prior to CPB (SURG), during rewarming from CPB (REWARM), after weaning from CPB (WEAN) and during early (REC-A) and late (24-48 hrs) recovery (REC-B). Binaural 500 Hz tones were presented via insert earphones. The EEG was recorded from Fz, Cz and Pz referenced to the right mastoid, with a band pass of 0.3 to 100 Hz. Averaging was used to increase signal-to-noise ratio. Epochs of 1.5 sec (1024 points) were employed. ASSR amplitude and phase were measured on the Cz channel using Fast Fourier Transform. Statistical analysis was performed using one-way ANOVA for repeated measures, Tukey's HSD and Rayleigh's test for phase coherence (4,5). The criterion for significance was $P < 0.01$.
Results: Mean total sufentanil dose was 9.6 ug/kg. Four patients required vasodilators for hypertension; one required propranolol for tachycardia.
The ASSR amplitude was significantly reduced (Table) during IND-B, SURG, REWARM and WEAN relative to BASE. During VENT and REC-A the amplitude reduction relative to BASE nearly reached significance ($0.01 < P < 0.05$). Phase coherence (Figure) was maintained across subjects during all stages ($P < 0.01$) except REWARM (NS) and WEAN ($0.01 < P < 0.05$). The ASSR response was clearly distinguishable relative to adjacent frequencies on the amplitude spectra (Figure) during all stages except REWARM.

TABLE

Period	Amp (uV)(SD)	Phase (deg)(SD)
BASE	.31 (.17)	14 (45)
IND-A	.25 (.11)	19 (29)
IND-B	.11 (.04)*	11 (48)
VENT	.12 (.07)	3 (62)
SURG	.10 (.06)*	9 (66)
REWARM	.08 (.02)*	-12 (76)
WEAN	.11 (.04)*	7 (68)
REC-A	.13 (.05)	5 (46)
REC-B	.16 (.07)	5 (16)
	$P < 0.001$	NS

* Significantly less than BASE ($P < 0.01$)

Discussion: Phase coherence and spectral analysis indicate that the ASSR, despite the amplitude reduction, was preserved during all periods except REWARM. The ASSR during sufentanil anesthesia resembles that produced by low intensity stimuli during normal sleep (2). This contrasts with isoflurane (0.9 MAC) anesthesia which abolishes the ASSR (3).

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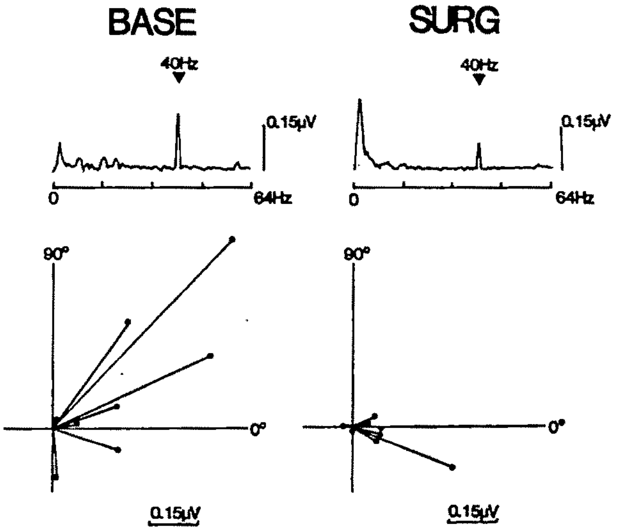
Supported by MRC, FRSQ, CAS Sheridan and FARQ awards.

FIGURE



RECORDINGS FOR BASE AND SURG.
The amplitude spectra of the average waveforms for all patients are shown on top. The 40 Hz peak (opposite filled triangle) is reduced during surgery. Polar plots depicting responses from individual patients are shown below. The amplitude of the response is represented by vector length; the phase, an index of ASSR latency, by the angle between the vectors and the zero degree line. The probability of phases being randomly distributed between 0 and 360 degrees, calculated by phase coherence analysis, was less than 1% ($P < 0.01$). By contrast, the phases would be randomly distributed if no response were present.

Title PLASMA SUFENTANIL LEVELS IN PEDIATRIC OUTPATIENTS RECEIVING NASAL PRE-INDUCTION OF ANESTHESIA

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Introduction: Nasal administration of sufentanil to pediatric ambulatory surgery patients has been recommended because it does not require a painful IM injection, it has a rapid onset and allows patients to be easily separated from their parents.[1] Little is known, however, about the pharmacokinetics of sufentanil absorbed through the nasal mucosa. We determined the serum levels achieved after nasal administration of sufentanil in a dose of 2 ug/kg. It is anticipated that this information will enable the definition of a safe dose by examining the plasma levels and elimination half-life.

Methods: With approval from the Committee for the Protection of Human Subjects, a prospective study was undertaken in 15 ASA I and II children scheduled for outpatient surgery between the ages of 18 months and 11 years. Surgical cases included herniorrhaphies, hypospadias repair, circumcision, and tonsillectomy. All procedures lasted over one hour. After obtaining informed parental consent, these unpremedicated patients were brought to a holding area where they received 2 ug/kg of nasal sufentanil with parents present. Sufentanil was given as nose drops from a tuberculin syringe while the child's head was held in the supine position. The child was separated from the parents 10 minutes after they received the nasal sufentanil. Patients were taken to the operating room where a mask induction was performed with nitrous oxide and halothane. An IV was established and 15 minutes after sufentanil administration 3ml of blood was drawn and placed in heparinized tubes. All patients received a nondepolarizing muscle relaxant and after controlled ventilation with 100% oxygen, the trachea was intubated and the stomach contents suctioned. Anesthesia was maintained with the same agents used for induction. No further narcotics were given. Three ml blood samples were drawn at 30, 60, 90, 120, and 150 minutes post sufentanil administration. All patients were extubated in the operating room at the completion of surgery. After an initial recovery period in the postanesthesia recovery room (PAR), children returned to day surgery unit (DSU) until discharged. Age, weight, sex, sufentanil dose, willingness to separate from parents, ease of induction, and the anesthesiologist's subjective assessment of ventilatory compliance (the ease of delivering positive pressure ventilation after the patient lost consciousness) were noted. Plasma was separated from venous blood samples by centrifugation and frozen at -20°C. Samples were analyzed by mass spectrometry using Hewlett Packard method modified after Woestenboughs, 1987. The pharmacokinetic data was analyzed with a model-dependent computation using a non-linear regression. A computer adaptation of a manual technique for exponential stripping (RSTRIP) was used to obtain initial monoexponential estimates.[2] The decay curves were fitted to the plasma concentration data with a non-linear square program. The decay curve for sufentanil concentration vs time (from 0 to 150 minutes) for each patient was fitted to a monoexponential curve by a modified Marquardt algorithm[3] and RSTRIP.

Results: Because peak plasma concentrations may have occurred before the first sampling time, we could only describe the elimination phase of the nasal sufentanil. In our patients the sufentanil concentrations declined mono-exponentially over 150 minutes (see Figure 1). The apparent elimination half-life was 74 minutes (with a standard error of 7.3 minutes) between 15 and 150 minutes after administration. The highest plasma level of sufentanil reached was approximately 0.3ng/ml, which occurred 15 minutes after nasal administration. The

were sedated, easily separated from their parents and received a smooth mask induction. One patient was difficult to separate from parents and received a stormy mask induction. No patient was judged as having decreased compliance to ventilation and none of the patients had prolonged stays in the PAR or DSU. No patient required analgesic medication in the PAR. Four patients experienced postoperative emesis.

Discussion: The absorption of sufentanil from the nasal mucosa appears to be quite rapid, reaching a mean level at 15 minutes of approximately 0.3ng/ml. Thereafter, it is rapidly eliminated, which compares favorably with IV sufentanil studies which used a three-compartment open model.[4,5] In these studies moderate (5 ug/kg) and high (12 ug/kg) dose intravenous sufentanil had elimination half-lifes of 164± 22 minutes and 12.1± 5.8 hours respectively. The short elimination half-life in our study may have been due to 1) the small total dose used; 2) duration of sampling for drug content was 150 minutes (vs 8 hours and 24 hours) and the magnitude of the elimination half-life may therefore have been underestimated; 3) the volume of distribution in the steady state of sufentanil increases significantly with age, as a result the elimination half-life also increases (average age in previous studies was 68 years vs 5 years in our study). Our study demonstrates that nasal sufentanil in a dose of 2 ug/kg facilitates separation from parents, provides for a smooth induction of anesthesia, and provides a good narcotic base for balanced general anesthesia. Furthermore, these patients are awake but appear analgesic 2-3 hours later when they are discharged from the DSU. These clinical observations correlate with laboratory verification of rapid absorption and elimination of sufentanil when administered to children nasally.

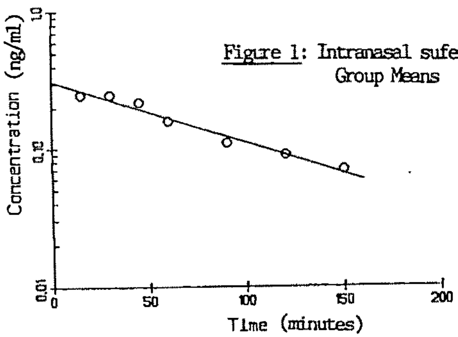

Figure 1: Intranasal sufentanil: Group Means

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TITLE: PARENT-ASSISTED "PCA" FOR POSTOPERATIVE PAIN CONTROL IN YOUNG CHILDREN

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INTRODUCTION: The use of Patient Controlled Analgesia (PCA) has been previously reported in children and adolescents 11 years of age or older.[1-3] We report the establishment of a Parent Assisted "PCA" program for the management of postoperative pain in young children.

METHODS: With parental and institutional approval, 22 consecutive patients 5-10 years of age were enrolled in this study. Parents and patients were instructed in use of the PCA pump (Abbott Lifecare$^{(R)}$), pain scales and how to properly complete data sheets. This program allowed the child and his/her "rooming-in" parent to jointly determine when the child's pain was sufficiently intense to require activation of the PCA system. With Parent-Assisted PCA, more time was spent screening the parent for intelligence and reliability than the child. An anesthesiologist evaluated patients for pain in the recovery room, and IV morphine sulfate (MS) was titrated until patients reported that they were comfortable. PCA maintenance therapy was then instituted using an initial MS dose of 0.02 mg/kg and a lockout interval of 15 minutes. Based upon patient's verbal feedback, Objective Pain Scores, and nursing observations, an anesthesiologist adjusted the initial settings by changing the demand-dose or the lockout interval in order to obtain maximum analgesia with minimum adverse effects.

The following additional data were recorded; age of child, surgical procedure, duration of PCA analgesia, degree of sedation, and morphine utilization expressed as mg/kg/hr. Each child's morphine utilization was plotted over time, and the slope of the line common to the morphine utilization of all children was determined. This common slope was then compared to a horizontal line (no slope) by ANACOVA. Parents and patients were interviewed at the completion of treatment to ascertain their satisfaction and to evaluate the stress that this treatment modality placed upon them.

RESULTS: The ages of the children ranged from 5 to 10 years (mean age 7.7 ± 1.8). PCA was used to provide postoperative analgesia following 5 orthopedic cases (23%), 12 abdominal surgeries (54%) and 5 non-cardiac thoracic procedures (23%). None of the children in the series experienced any sign of respiratory distress; however, 3/22 children or their rooming-in parent (14%) did experience difficulty in either operating or understanding when to use the pump. Four other children (18%) were troubled by narcotic-related complications, such as: constipation, nausea, itching and pain at their IV site. None of the complications were severe enough to require discontinuation of PCA therapy. Twenty patients utilized the PCA device for 24 hours or longer starting on the evening of surgery and continuing through the night of the 2nd postoperative day. The common slope of the morphine utilization for these children expressed as mg/kg/hr. plotted against time was -0.0002. This slope differs from a line with zero slope (no tendency to wean) in a highly significant manner ($p < 0.001$), and clearly reflects the tendency of these children to rapidly wean themselves from PCA (table).

MORPHINE UTILIZATION EXPRESSED AS
mg/kg/hr*

Postop Day	Nursing Shift	n	PCA Morphine Mean (± SD)
DOS	Eve	21	0.040 (0.053)
1	Night	21	0.022 (0.020)
	Day	20	0.025 (0.018)
	Eve	20	0.021 (0.013)
2	Night	20	0.014 (0.007)

*Morphine utilization for one child not recorded on PCA sheet.

Only one parent reported the PCA experience to be exceptionally stressful. She offered the following comments "I didn't like to see my child doped up. At night he did not wake up enough to push the button; I finally figured out if I pushed the button twice in an hour he was OK, but I was exhausted. However, overall, I was happy to take part in the study." All other parents had only positive comments. Many of them reported that PCA reduced their level of stress by allowing them to have control over their child's narcotic administration schedule and by providing them with a means to promptly decrease their child's pain.

DISCUSSION: This series demonstrates that children as young as 5 years of age can safely and efficaciously use PCA with the help of a "rooming-in" parent. Most patients in this series obtained excellent analgesia with minimal sedation. Side-effects inherent to narcotic therapy were encountered in 18% of the children but would have likely been experienced if equipotent narcotic dosages had been administered IV/IM prn. The 3/22 (14%) children or parents who encountered difficulty in using the pump or in following instructions points out that PCA may not be the preferred treatment modality for all families. Like their older counterparts, these young children showed a tendency to decrease their narcotic utilization over time.[1,4] This observation reinforces our belief that even young children understand varying pain intensities, and that they only use narcotic analgesics to control their pain to an acceptable level and not to eradicate it.

In summary, PCA is suitable for the management of postoperative pain in young children who have pain requiring narcotic analgesia.

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Title: COMPARISON OF HEMODYNAMIC STABILITY DURING AORTIC CROSS-CLAMPING USING TRANSDIAPHRAGMATIC ECHO

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Introduction: The ideal anesthetic for surgery involving cross-clamping of the aorta should maintain myocardial performance, without compromising the integrity of the peripheral vascular system. Traditional techniques depress myocardial function and/or blunt the sympathetic tone of the peripheral vascular system. Epidural morphine with light general anesthesia provides surgical anesthesia without impairing myocardial function or sympathetic tone.

Methods: After obtaining approval from the Human Subjects Review Committee, 21 patients who underwent surgery for repair of diseased aortas were divided evenly between 4 anesthetic groups: epidural morphine with 70% N_2O (MS), nitrous-narcotic with fentanyl (Fent), inhalational using isoflurane and 100% oxygen (Inh), or epidural bupivacaine with 70% N_2O (Bup). Transdiaphragmatic ECHO of the left ventricle (LV) was performed during aortic cross-clamping using a Hewlett-Packard probe. LV short axis areas were directly measured, and LV volumes were calculated using a modified model of a single plane LV axis at the papillary muscle.

Results: Those patients who had epidural morphine during the surgery proved to have the least hemodynamic changes. In addition they had less LV changes compared to other groups ($p<0.05$).

Discussion: Acute changes in LV volume, in response to severe afterload increases at aortic cross-clamping, are an indication of impending LV strain. Our data show, surprisingly, that the area and volume changes are least in the epidural morphine group. Regional local anesthesia and inhalational anesthesia, which have the most potential for producing systemic vascular changes, did not produce the same salutory changes as epidural morphine. Nitrous-narcotic anesthesia with fentanyl, a commonly used anesthetic for aortic surgery, produced far greater changes than any other group.

Conclusion: The anesthetic technique with the least changes in LV volume seems to be the most preferable. Therefore, we recommend epidural morphine for aortic surgery involving acute changes in LV afterload.

ANESTHETIC TECHNIQUE

	MS	Fent	Inh	Bup
Systolic area changes (%) (n=7)	3	18	3	5
Diastolic area changes (%) (n=7)	3	4	7	4
Cardiac output changes (%) (n=21)	7	11	11	10

Title: DOES RESIDENCY TRAINING COMPROMISE PATIENT SAFETY?

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Introduction: The issues of quality assurance in the current atmosphere of peer review reimbursement and medical liability have provided increasing pressure to define and assess the quality of medical care at the local level. In a university hospital where physicians under training participate in patient management, it is all the more necessary to identify avoidable incidents and try to eliminate their cause. We did a retrospective study of avoidable incidents that occurred in our institution. We compared the incidence of avoidable errors among residents with the same among a group of nurse anesthetists who are also practising in our institution under identical circumstances.

Methods: The data was obtained from the computerized data base whch we use in our department to collect and analyze critical incidents that occur during the course of an anesthetic. The reporting of critical incidents was voluntary and based on guidelines issued by the Departmental Quality Assurance Committee, which consists of three faculty anesthesiologists, one anesthesia resident and two CRNAs, reviewed all the reported incidents and classified them as avoidable or unavoidable, based on a previously agreed upon definition.

Results: A total number of 3481 cases were done during a seven month period. 36% of these cases were "high risk," i.e., ASA 3 or higher and emergencies belonging to any classification.

TABLE I

	Overall	Residents	CRNAs
Total Cases	3481	58%	42%
Reported Incidents	181	114 (63%)	67 (37%)

TABLE II

	Reported Events	High Risk Cases	Unavoidable Events	Avoidable Events
Overall	181	89	166 (97.1%)	15(8.3%)
Residents	114	55 (62%)	104 (91.2%)	10(8.8%)
CRNAs	67	34 (38%)	62 (92.5%)	5(7.5%)

As can be seen from Tables I and II, the incidence of avoidable errors was not very much different between the two groups of practitioners. Residents reported a greater number of critical incidents, but they were working on higher risk cases. Considering that CRNAs are trained individuals and residents are still in training, it would be reasonable to state that the process of training has not jeopardized patient safety in our institution.

TITLE: LOW-DOSE DROPERIDOL VS. STANDARD-DOSE DROPERIDOL FOR PREVENTION OF VOMITING AFTER PEDIATRIC STRABISMUS SURGERY

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AFFILIATION: Departments of Anesthesia and Ophthalmology, Bowman Gray School of Medicine, Wake Forest University Medical Center, Winston-Salem, North Carolina

Introduction:

Pediatric strabismus repair, a common out-patient surgical procedure, is frequently complicated by postoperative nausea and vomiting with a reported incidence of 30-80%.[1-5] This complication occurs regardless of anesthetic technique. Vomiting after surgery, if persistent, may upset electrolyte balance, cause dehydration, and prolong hospitalization. Droperidol, a butryophenone, has been shown to reduce the incidence of vomiting dramatically after strabismus surgery. Studies have suggested that 75 mcg/kg are required for adequate antiemetic action.[3] In our experience, this standard dose sedates children and makes ophthalmological evaluation difficult postoperatively. Lower doses of droperidol are routine in adults and have demonstrated efficacy in some pediatric patients.[6] We compared the higher dose of droperidol (75 mcg/kg) with a lower dose (20 mcg/kg) to evaluate efficacy of the lower dose in preventing nausea and vomiting after strabismus surgery. We also evaluated differences in length of hospitalization associated with these 2 regimens as well as problems with the postoperative strabismus evaluation.

Methods:

The study was approved by the Institutional Review Board. One hundred ASA I and II children, ages 2-18, were studied after informed consent was obtained from parents for this double-blind study. Patients with superimposed medical disease or with medical problems predisposing to nausea and vomiting were excluded. No child was premedicated. Anesthesia was induced by mask halothane or intravenous pentothal. All maintenance anesthetics were with halothane, N_2O, and O_2. Muscle paralysis was with pancuronium. Preoperative fluid deficit was completely replaced in all patients before discharge from the Post-Anesthesia Care Unit (PACU). The stomach was decompressed prior to extubation. Droperidol (75 µg/kg), droperidol (20 µg/kg) or saline were injected intravenously at the beginning of each case.

Vomiting was assessed by masked nursing staff in the PACU and the ambulatory surgery center. Ease of examination was evaluated by the attending Ophthalmologist in his office after the patient was discharged. The eye evaluation included an attempt to assess fixation in young children, visual acuity in older children, measurement of strabismus at distance and near, and ocular versions.

The data were analyzed using analysis of variance and chi-square analysis.

Results:

There were no statistical differences among the three groups regarding age, weight or preoperative fluid deficit.

Vomiting occurred in 39 patients. Eighteen were in the saline control group with the other 21 evenly divided between the 75 µg/kg and the 20 µg/kg groups. The incidence of an unsatisfactory exam was the same in all groups, as was the incidence of a delay greater than one hour in the PACU. The time from the end of surgery to arrival in the PACU was virtually the same in all groups. There was a tendency for a prolonged recovery room stay in those children receiving 75 µg/kg.

Although statistical significance was not attained in the analysis of nausea and vomiting (p=.0521), the results were strongly suggestive of a clinical effect.

Discussion:

The efficacy of droperidol for prevention of post-strabismus surgery vomiting has been studied repeatedly. Abramowitz et al found a dose of 75 µg/kg effective in reducing the incidence of vomiting to 43%.[3] Eighty percent of patients in the control group for this study vomited. In the present study less than 50% of patients vomited regardless of treatment. Those patients treated with droperidol vomited less than 35% of the time; there were no differences between standard dose and low dose droperidol in the incidence of vomiting.

We feel that conservative management of children during and after strabismus surgery, involving postoperative suctioning of gastric contents, complete replacement of pre-operative fluid deficits, avoidance of narcotics, as well as a small dose of droperidol (20 µg/kg) is a reasonable approach to the care of these patients.

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	Droperidol 75 µg/kg	Droperidol 20 µg/kg	Saline
Vomited %	29.4	34.3	52.9*
Prolonged PACU Stay %	11.7	6.2	8.8
Unsatisfactory Eye Exam %	17.6	15.6	11.7

*Different from both Droperidol groups (P=.0521) by Fischer's Exact Test.

TITLE: EFFECT OF TETANUS ON TRAIN-OF-FOUR: POTENTIATION AND TIME TO RECOVERY

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INTRODUCTION: Anesthesiologists commonly employ train-of-four (TOF) monitoring to assess the degree of neuromuscular blockade.[1] Not uncommonly, the anesthesia care provider will supplement such monitoring with a tetanic stimulus. It has long been postulated that such a stimulus may exert subsequent effects on the neuromuscular junction.[2] The present study sought to determine the influence of a 5 sec tetanus on serial TOF monitoring.

METHODS: After Human Investigation Committee approval, 21 patients undergoing general anesthesia were studied. A peripheral nerve stimulator (Digistim III, Neuro Technology, TX) calibrated to deliver a 50 mA stimulus was applied to the patient via cutaneous electrodes over the olecranon groove and volar forearm. The ipsilateral thumb was placed into a force transducer (Adductor Pollicis Monitor, Medar Corp., NY) which was interfaced to a stripchart recorder. After induction of anesthesia, neuromuscular blockade was maintained with a vecuronium infusion to achieve a T_4/T_1 ratio of 0.2 to 0.8. Once TOF monitoring at 10-sec intervals remained stable for five minutes, a tetanic stimulus was applied for five seconds. TOF monitoring was resumed 10 seconds later and continued at 10 second intervals until T_4, T_1 and T_4/T_1 each returned to within 10% of baseline. Four tetanic stimuli were delivered: A) an initial 50 Hz tetanic stimulus; B) a second 50 Hz tetanus at 2 minutes after the previous T_4, T_1 and T_4/T_1 returned to baseline; C) an initial 100 Hz stimulus at 3 minutes after recovery from B; D) a second 100 Hz stimulus at 2 minutes after recovery from C.

Following each tetanic stimulus, the percent potentiation of the first TOF response was determined for T_1, T_4 as well as T_4/T_1 and compared with Wilcoxon signed rank test. Times to recovery were analyzed in a similar fashion. The potential effect of the first tetanus at 50 Hz (A) on the second test series (B) was analyzed with paired t-test. The effects of previous testing at 100 Hz (C) on series D were analyzed similarly. Data are presented as mean ± SD. A value of $p<0.05$ was considered significant for all analyses.

RESULTS: The data are summarized in the Table. There was no apparent effect of a tetanus on subsequent test periods. Thus, the two series at the same frequency could be grouped together (i.e., A+B and C+D). After 50 Hz (A+B), there was 52% mean potentiation of T_1 (12.8 mm to 18.6 mm), 493% mean potentiation of T_4 (3.6 mm to 13.0 mm) and 265% mean potentiation of the T_4/T_1 ratio (0.31 to 0.81) ($p<0.001$ for pre- vs post-tetanus values of T_1, T_4, T_4/T_1). The recovery times averaged 43.0, 51.3 and 47.9 seconds for T_1, T_4 and their ratio, respectively ($p<0.05$ for T_4 vs T_4/T_1). After 100 Hz (C+D), there was 49% potentiation of T_1, 579% potentiation of T_4 and 346% potentiation of T_4/T_1 ($p < 0.001$ for pre- vs post-tetanus values). The recovery times averaged 75.5, 87.8 and 78.4 seconds ($p<0.05$ for T_4 vs T_4/T_1). The potentiation of T_4/T_1 after 100 Hz was significantly greater than that after 50 Hz. After both the 50 and 100 Hz tetanic stimuli, the potentiation of T_4 was significantly greater than that of T_1.

DISCUSSION: The findings are reassuring in that they suggest serial TOF monitoring can be continued in the presence of intermittent tetanic stimulation. Following tetanus at 50 Hz, T_4/T_1 recovered within approximately 48 seconds. The longer time to recovery after 100 Hz (81 sec) was consistent with the greater potentiation seen after this more intense stimulus.

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Potentiation % and Recovery Times (sec)

	T_1	T_4	T_4/T_1
A: First 50 Hz			
% Potent.	50.2±42.6	499.6±462.4	276.0±228.0
Rec. Time	41.3±19.2	52.4± 16.4	50.4± 16.7
B: Second 50 Hz			
% Potent.	53.8±41.5	484.2±548.1	250.2±241.9
Rec. Time	45.3±20.6	49.9± 13.4	44.5± 15.2
A+B: Both 50 Hz			
% Potent.	51.7±41.6	493.2±492.3	265.2±230.9
Rec. Time	43.0±19.6	51.3± 15.0	47.9± 16.1
C: First 100 Hz			
% Potent.	45.5±32.9	542.6±420.2	337.4±282.8
Rec. Time	77.8±44.9	83.5± 26.4	77.1± 27.7
D: Second 100 Hz			
% Potent.	54.4±44.0	633.0±498.9	358.8±271.1
Rec. Time	70.0±33.9	95.8± 35.8	80.8± 34.8
C+D: Both 100 Hz			
% Potent.	49.1±37.1	578.8±445.4	345.9±272.7
Rec. Time	75.5±41.0	87.8± 29.5	78.4± 29.4

TITLE: COMPARISON AND CORRELATION OF TRAIN-OF-FOUR AND DOUBLE BURST STIMULATION RATIOS

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INTRODUCTION: The most clinically used method of assessing depth of neuromuscular blockade is assessment of fade to train-of-four (T_4/T_1) stimulation. Unfortunately, tactile and visual assessments of fade are unreliable, especially when the T_4/T_1 ratio is between 0.4 and 0.7.[1] Electromyographic and mechanographic instrumentation has been recommended as an aid for assessment, but tends to be impractical in the clinical setting. Recently, double burst stimulation (DBS) has been proposed to facilitate tactile detection of fade.[2] DBS consists of two high-frequency (50 Hz) sets of impulses separated by 750 msec. Each set consists of impulses of 0.2 msec in duration at 20 msec intervals. $DBS_{3,3}$ incorporates 3 impulses followed by an additional 3, whereas $DBS_{3,2}$ incorporates 3 impulses followed by 2. The present prospective study employed a mechanogram to compare assessment of neuromuscular blockade by DBS with assessment by T_4/T_1, during continuous vecuronium infusion.

METHODS: After approval by the institutional Human Investigation Committee, 20 patients undergoing general anesthesia were evaluated. After induction of anesthesia, the ulnar nerve was stimulated via cutaneous electrodes with a Myotest (Biometer, Denmark) nerve stimulator, which was calibrated to deliver a 50 mA stimulus. The negative electrode was placed over the olecranon groove, and the positive electrode on the volar forearm. Neuromuscular response was assessed with an adductor pollicis monitor (Medar Corp., NY), interfaced to a stripchart recorder. Patients were given a continuous infusion of vecuronium, until T_4/T_1 remained constant for at least 5 minutes. DBS responses were recorded over a wide range of T_4/T_1 ratios (0.2 to 1.0). T_4/T_1, $DBS_{3,2}$ and $DBS_{3,3}$ were then administered in random order, at two minute intervals. The two bursts of DBS were measured and termed D_1 and D_2 respectively. The T_4/T_1 ratio, D_2/D_1 for $DBS_{3,2}$, and D_2/D_1 for $DBS_{3,3}$ then were calculated. Data were analyzed with linear regression; $p<0.05$ was considered statistically significant.

RESULTS: As noted in Figure 1, there was a significant linear correlation between T_4/T_1 and D_2/D_1 of $DBS_{3,2}$ ($p<0.0001$). The same significant linear correlation was obtained between T_4/T_1 and D_2/D_1 of $DBS_{3,3}$. For this comparison, the regression equation was: $y = 0.043 + 0.942X$, $r^2 = 0.94$. The regression equations indicate that a T_4/T_1 ratio of 0.70 corresponds to 0.57 for $DBS_{3,2}$ and 0.70 for $DBS_{3,3}$.

DISCUSSION: The present data suggest that the relationship between the D_2/D_1 and the T_4/T_1 ratios is linear throughout a wide range of T_4/T_1 values. Each of the three methods ($DBS_{3,2}$, $DBS_{3,3}$, and TOF) should be reliable for quantitative assessment of blockade. However, DBS is more reliable than T_4/T_1 monitoring for detection of fade by qualitative tactile discrimination.[2,3] This is partly due to the fact that DBS does not entail two intervening twitches (i.e., T_2 and T_3) between the points of comparison. The difference between $DBS_{3,2}$ and $DBS_{3,3}$ is due to the former's less intense second burst.

It is classically taught that a T_4/T_1 ratio of greater than 0.70 is desirable before extubating a patient who has received a neuromuscular blocking agent. Our data suggest that, at 50 mA, a $DBS_{3,2}$ D_2/D_1 ratio of approximately 0.6 and a $DBS_{3,3}$ D_2/D_1 ratio of approximately 0.7 correspond to this cutoff.

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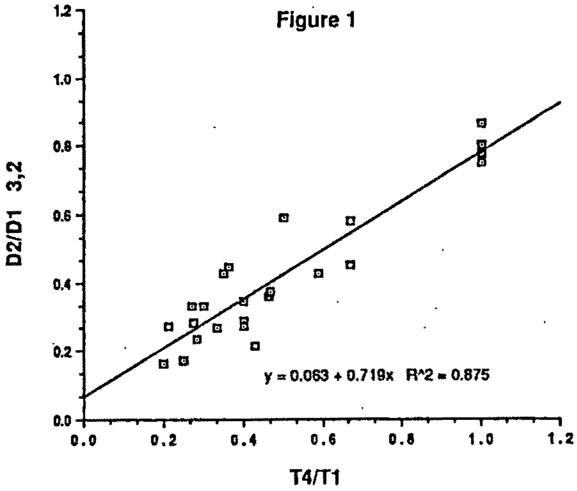

Figure 1

TITLE: EFFECT OF TETANUS ON SUBSEQUENT DOUBLE BURST STIMULATION RESPONSES

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INTRODUCTION: A new method of nerve stimulation, introduced to improve tactile detection of clinically relevant residual blockade, has been termed "double burst stimulation" (DBS).[1,2] This consists of two high-frequency sets of impulses separated by 750 msec. Each set consists of impulses 0.2 msec in duration at 20 msec intervals (50 Hz). $DBS_{3,3}$ incorporates 3 impulses followed by an additional 3, whereas $DBS_{3,2}$ incorporates 3 impulses followed by 2 impulses. We termed the first neuromuscular response D_1 and the second D_2. Traditionally train-of-four (TOF) stimulation has been employed clinically to evaluate the degree of neuromuscular relaxation. DBS has been recommended as an improvement over TOF, because DBS fade is more readily detected without a mechanogram.[1] Since many anesthesiologists supplement serial TOF monitoring with intermittent tetanic stimulation, we sought to determine the effect of tetanus on subsequent responses to DBS.

METHODS: Following approval of the institutional Human Investigation Committee, 20 patients undergoing elective surgery were evaluated. The ulnar nerve was stimulated with a calibrated Myotest (Biometer, Denmark) monitor. The negative terminal of the cutaneous electrode was placed over the olecranon groove, and the positive electrode was on the volar forearm. The patient's thumb was inserted into a calibrated adductor pollicis monitor (Medar Corp., NY) that was interfaced to a stripchart recorder, in order to quantify DBS neuromuscular responses. Patients were given a continuous infusion of vecuronium. Once a DBS ratio (D_2/D_1) was within the 0.2 to 0.8 range and remained constant for at least 5 minutes, 50 Hz tetanus was applied to the ulnar nerve for 5 seconds. The potentiation of DBS at 20 sec was determined, and readings were continued every 20 sec until the heights of D_1 and D_2, as well as the D_2/D_1 ratio, recovered to within 10% and/or 0.5 mm of pre-tetanic baseline. This protocol was followed for both $DBS_{3,3}$ and $DBS_{3,2}$, with each of two determinations per patient in random sequence (five minutes after recovery). The data were analyzed by Wilcoxon figured rank test, and are expressed as mean ± SD, with $p<0.05$ considered statistically significant.

RESULTS: For $DBS_{3,2}$, there was 69%, 535%, and 284% potentiation of D_1, D_2, and D_2/D_1 respectively at 20 sec after tetanus (Table) ($p<0.001$ for pre- vs post-tetanus values of D_1, D_2, D_2/D_1). Recovery of these indices was noted at 50.3, 52.8, and 35.0 seconds after tetanus ($p<0.01$ between D_1 and D_2/D_1, $p=0.03$ between D_2 and D_2/D_1). For $DBS_{3,3}$, there was 53%, 323% and 161% potentiation ($p<0.001$ for pre- vs post-tetanus values); recovery times were 45.0, 52.1 and 45.0 seconds ($p>0.05$). The potentiation of D_2 was greater than that for D_1 for $DBS_{3,2}$ and $DBS_{3,3}$ ($p<0.001$).

DISCUSSION: Consistent with its effect on TOF, tetanus causes an increase in the magnitudes of D_1 and D_2, as well as an increase in the D_2/D_1 ratio. The duration of these changes, when tested every 20 sec, is less than two minutes. The greater relative potentiation of D_2 compared to D_1 may be attributed to its potentiation by the combination of both the tetanic stimulus and D_1; this was most marked when the second burst consisted of only two impulses (i.e., $DBS_{3,2}$).

It is evident that the post-tetanic facilitation of either $DBS_{3,2}$ or $DBS_{3,3}$ is a relatively short-lived phenomenon. It is reassuring from a clinical standpoint that a tetanic stimulus will not alter DBS responses for longer than two minutes when DBS is continued at 20 second intervals; further DBS responses after this time will remain accurate. We conclude that tetanus can be utilized along with DBS when evaluating neuromuscular function.

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	$DBS_{3,2}$	$DBS_{3,3}$
% Potentiation		
D_1	68.75± 65.96	52.97± 53.51
D_2	534.57±500.50	323.30±265.44
D_2/D_1	284.37±296.19	160.77± 75.40
Recovery Time (sec)		
D_1	50.26± 13.07	45.00± 17.89
D_2	52.06± 14.04	51.25± 12.04
D_2/D_1	35.00± 14.61	46.43± 12.31

TITLE: EXTENT OF DIFFERENTIAL SENSORY BLOCKADE WITH EPIDURAL ANESTHESIA
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INTRODUCTION: Spinal anesthesia is associated with zones of differential blockade.[1] The reason for their existence is multifactorial and includes fiber size, presence of myelin, conduction frequency, location of fiber within the nerve bundle. Alternatively, the existence of zones of differential blockade during epidural anesthesia is more controversial.[2,3,4]

The present study was undertaken in order to determine the existence and, if so, the extent of zones of differential sensory blockade during clinical epidural anesthesia.

METHODS: After approval by the institutional Human Investigation Committee, 17 patients scheduled for non-emergent surgical procedures were investigated. Epidural anesthesia was achieved in all cases with 2% lidocaine with 1:200,000 epinephrine plus 0.1 mEq/cc sodium bicarbonate. The dosing intervals were not prescribed by the study, as they were determined by the anesthesia care provider. Mean total dose of 25.88 cc was given over 30 min, with 7.47 cc of the total dose being given in the first 5 minutes.

The dermatomal levels of blockade of light touch (LT), pinprick (PP), temperature discrimination (T), as well as blood pressure (BP) and heart rate (HR) were measured every 5 min after onset of epidural anesthesia, up to 30 minutes.

LT was measured by applying the dull end of a safety pin to the skin without indenting it. PP was measured using the sharp tip of a sterile safety pin. T was measured by spraying the skin with a non-toxic, non-flammable, highly-volatile agent (Fluori-Methane, Gebauer). BP was measured with a sphygmomanometer, and HR was determined by electrocardiogram.

Data were analyzed by ANOVA and chi-square tests and expressed as mean ± SD, with $p<0.05$ statistically significant.

RESULTS: The most cephalad dermatomal levels occurred at thoracic (Th) 4.86±2.54 for LT, at Th 3.45±1.86 for PP, and Th 1.92±2.50 for T ($p<0.05$ for LT vs PP, PP vs T, LT vs T). The onset times of the zones of sensory differentiation reached statistical significance by 5 min, such that at 5 min, the LT-PP zone had a mean of 1.00±0.58, and the PP-T zone had a mean of 1.27±0.65. These differences persisted over the next 25 minutes, as the level for each sensory modality progressed cephalad (Fig. 1).

During the study period, the mean differences of LT-PP and PP-T zones were not statistically different from each other.

Mean diastolic blood pressure (mmHg) showed a significant decrease over time, from 95.6 (baseline), to 80.9 at 30 minutes. Conversely, mean HR increased over time from a baseline of 76.4 to 85.6 at 30 minutes.

DISCUSSION: Epidural, like spinal anesthesia, appears to be associated with zones of differential sensory blockade. Their existence is in contradistinction to previously reported findings.[2] The onset time of the differential zones appears to be 5 min or less, as this is when the LT-PP and PP-T differences reach statistical significance. Once established, these zones appear to remain statistically constant over time.

Interestingly, although there were no significant differences between zones, there is a tendency of the LT-PP zone to increase over time from 1.0±0.58 dermatomes (at 5 min), to 2.31±1.54 dermatomes at 30 min ($p=0.25$).

Mean BP shows a progressive decline over time, as the level of sympathetic blockade progresses cephalad, and the HR increases over time.

In conclusion, epidural anesthesia with carbonated lidocaine plus epinephrine appears to be associated with equal and constant zones of differential sensory blockade, and patients evidence hemodynamic changes indicative of sympathetic blockade.

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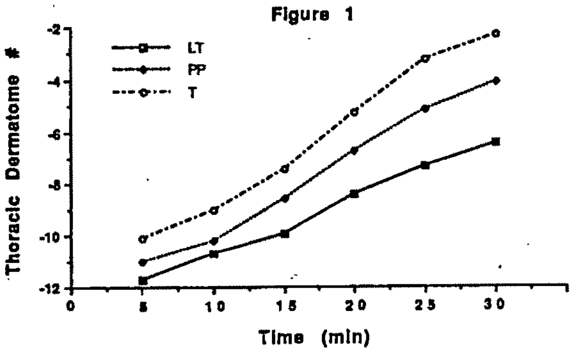
Figure 1



TITLE: CEREBROVASCULAR RESPONSES TO SUFENTANIL CITRATE (SC) IN PRIMATES WITH AND WITHOUT INTRACRANIAL HYPERTENSION

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Introduction: Sufentanil Citrate (SC) is a new, relatively potent, synthetic narcotic analgesic that has been recommended for the anesthetic management of both cardiac and neurosurgical patients. It has been assumed that SC, like its analogue fentanyl citrate (FC), has similar effects on cerebral hemodynamics in terms of decreasing both cerebral blood flow (CBF) and cerebral metabolic rate ($CMRO_2$). Thus, it has been thought that SC could be used safely in patients having decreased intracranial compliance. Conflicting reports in animals and humans have recently surfaced concerning the cerebrovascular responses to SC. In dogs, a dose independent rise in CBF, an increase in intracranial pressure (ICP), and a fall in $CMRO_2$ was observed in both normal and non-compliant brains (Milde and Milde 1987, Milde and Milde 1989). In humans and rats, a dose dependent decrease in CBF and $CMRO_2$ was reported following SC (Keykhah et al 1985, Young et al 1988). The present study was designed to evaluate hemispheric CBF, ICP, and $CMRO_2$ in rhesus monkeys with normal and elevated ICP following SC administration.

Methods: The protocol for this study was approved by the Laboratory Animal Care Committee of the University of Texas Health Science Center at San Antonio. Thirty rhesus monkeys weighing between 4-6kg were sedated with 25mg/kg sodium thiopental, intubated and ventilated to maintain normoxia and normocarbia. Anesthesia was maintained with 1% halothane and a 50:50 mixture of nitrous oxide and oxygen. Animals were paralyzed with pancuronium bromide 0.05mg/kg. Arterial and venous pressures via the femoral vessels, EKG, and temperature were continuously monitored. A catheter was inserted into the cisterna magna percutaneously for ICP measurements. Two cranial burrholes were made, one over the left temporal lobe for controlling ICP with an epidural balloon catheter, the second over the sagittal sinus for insertion of a sagittal sinus catheter. A left ventricular catheter was also inserted retrograde from the femoral artery for radioactive microsphere analysis of CBF. A gas sampling catheter was positioned in the airway and attached to a mass spectrometer for end-expiratory gas analysis. ICP was elevated by inflating the epidural balloon so as to raise and maintain ICP at 30mmHg for at least 2hrs. prior to collecting data. SC was evaluated (in groups of 5 monkeys each) at 2.0, 5.0, 10.0 micrograms(ug) per Kg in monkeys with normal ICP; at 2.0ug/Kg with increased ICP; and at 5.0 ug/Kg in both normal and increased ICP using a neosynephrine infusion for blood pressure support. Measurements of CBF, ICP, MAP, and $CMRO_2$, were made prior to and at 5, 30, 60 minutes after SC injection. After completion of instrumentation, the halothane-nitrous oxide inhaled mixture was stopped and a mixture of 50% N_2 and 50% O_2 was started. SC was not injected until complete wash-out of nitrous oxide and halothane occurred. Data was evaluated by an analysis of variance followed by specific post tests with $p<0.05$ considered significant.

Results: (See Table below) A dose dependent fall in CBF and $CMRO_2$ ($p<0.05$) was observed following SC administration in the normal ICP groups, with both variables trending towards control by 60min. A concomitant fall in arterial pressure (AP) and CPP ($p<0.05$) was also observed with AP and CPP drifting upwards toward control by 60 min. No change in ICP was noted. In the elevated ICP group CBF and $CMRO_2$ also fell ($p<0.05$) 5min after SC and continued to decline out to 60min. AP and CPP fell after SC ($p<0.05$) and remained unchanged at 60 min. No change in ICP was noted. In the normal ICP group with AP support, CBF and $CMRO_2$ fell ($p<0.05$) 5 min after SC, with CBF remaining unchanged at 60min and $CMRO_2$ recovering to control values. AP and CPP also fell ($p<0.05$) recovering close to control by 60min. No change in ICP was noted. In the elevated ICP group with pressure support, no change in CBF was noted following SC. $CMRO_2$, however, was reduced ($p<0.05$) and remained unchanged at 60 min. AP and CPP also fell ($p<0.05$) 5 min after SC recovering by 60 min.

Discussion: The monkey appears to be exquisitely sensitive in terms of the blood pressure response to SC at the dose levels in this study. In spite of the marked hypotension induced by SC, cerebral autoregulation appears to be minimally affected and certainly not abolished at blood pressures often below the lower limits of autoregulation of cerebral blood flow. CBF and $CMRO_2$ appear to remain coupled in both normal and non-compliant brains, both changing similarly following SC administration. Contrary to previous reports, however, SC does not appear to significantly affect ICP.

	Normal ICP (2 ug/kg)				Elevated ICP (2 ug/kg)			
	C	5	30	60	C	5	30	60
MAP	117±5	40±3*	47±5*	58±7*	100±15	59±16*	70±18*	67±11*
ICP	11±0.5	9±1	9±0.7*	9±0.7	27±1	29±3	30±2	29±5
CPP	106±7	31±3*	38±6*	47±6*	73±15	31±15*	40±17*	38±9*
CBF	113.5±15.5	39.6±7.7*	39.9±9.0*	43.4±8.4*	101.8±20.1	27.4±6.2*	15.9±7*	11.6±7.2*
$CMRO_2$	3.4±1.0	2.0±0.4*	2.8±0.2*	2.1±0.5*	5.6±1.7	3.7±1.6	2.8±1.6*	2.7±1.7*

	(5 ug/kg)				Normal ICP w/BP support (5 ug/kg)			
	C	5	30	60	C	5	30	60
MAP	103±10	39±8*	49±10*	54±10*	134±2	89±7*	94±5*	104±4*
ICP	11±2	8±1	11±2	12±2	13±3	9±2	8±2	8±1
CPP	94±10	31±9*	38±11*	42±11*	121±3	80±7*	86±6*	96±5*
CBF	85.4±12.6	33.8±4.6*	35.2±6*	48.0±10.3*	131.6±27.2	63.2±17.2*	61.4±11.7*	83.4±19.2*
$CMRO_2$	3.8±1.0	2.3±0.3*	2.1±0.4*	2.5±0.5*	4.1±0.5	2.9±0.2*	3.1±0.2*	4.5±0.5

	(10 ug/kg)				Elevated ICP w/BP support (5 ug/kg)			
	C	5	30	60	C	5	30	60
MAP	110±6	37±3*	41±3*	54±2*	95±7	60±9*	78±6*	89±5
ICP	14±4	12±2	12±2	11±3	30±0.2	20±3*	20±5*	17±4*
CPP	96±6	25±3*	29±4*	43±3*	65±7	34±10*	58±10	72±8
CBF	123.9±25.0	48.1±2.8*	43.9±6*	62.5±6.1*	71.2±3.6	70.4±14.5	75.9±14.4	84.8±16.7
$CMRO_2$	4.7±1.5	2.1±0.3*	1.7±0.3*	2.4±0.4*	4.6±0.7	3.3±0.5*	3.0±0.3*	3.0±0.3*

Title: A COMPARISON STUDY OF SINGLE-DOSE VS. CONTINUOUS SUBARACHNOID BUPIVACAINE ANESTHESIA FOR TRANSURETHRAL PROCEDURES.

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Introduction: The technique of continuous subarachnoid anesthesia has been well described as a safe and effective method of providing surgical anesthesia, particularly in the medically compromised patient.(1) However, it has failed to gain widespread popularity secondary to unsubstantiated concerns of nerve root trauma and post-lumbar puncture cephalgia (PLPC), and the popularity of epidural anesthesia. The advantages of continuous subarachnoid anesthesia include rapidity of onset, minimal risk of anesthetic toxicity, profound motor blockade, and unlimited duration of action with shorter recovery room stays. These unique properties make this technique especially useful in the elderly population presenting for transurethral resection of the prostate (TURP) or transurethral resection of bladder tumors (TURBT). We therefore undertook the present study to characterize and compare the level of sensory blockade, the time to onset of pain and/or discharge from the recovery room, and the occurrence of complications in elderly male patients randomized to receive hyperbaric bupivacaine via an indwelling subarachnoid catheter or single-injection technique for TURP or TURBT.

Methods: Institutional Review Board approval was granted and written informed consent obtained from study participants. 18 patients were randomized to two separate groups. Group I received 2.3 ml (17.5 mg) of hyperbaric bupivacaine (0.75% in 8.25% dextrose and water; Winthrop) via a 22g spinal needle introduced at the L3-4 interspace in the right lateral decubitus position. Following the injection of bupivacaine, the patients were immediately repositioned in the low lithotomy position. Group II received 1 ml (7.5 mg) of hyperbaric bupivacaine through a 20g subarachnoid catheter (Burron, CE 18TK) in the lithotomy position. The catheter was inserted through an 18g Tuohy needle via the L3-4 interspace and positioned to leave only 2 cm within the subarachnoid space. Patients in Group I were also equipped with a sham catheter assembly in an effort to blind the observer and patient. Following the administration of the anesthetic, a blinded observer recorded the level of sensory anesthesia to pinprick at 5, 10, and 20 minutes, then every 20 minutes until the patient complained of pain or met criteria for discharge from the recovery area (full resolution of motor blockade). Patients were evaluated postoperatively for PLPC, paresthesias, or other complications.

Results: Study patients enrolled in Group I had a mean age (standard deviation) of 71 yrs (7.3) as compared to Group II 69 yrs (6.3), there were no significant differences in body habitus between the groups. Patients in Group I achieved a mean sensory level of T5 (2) with an average time to discharge from the recovery room of 234 (59) minutes. Despite a substantially smaller dose of bupivacaine, the patients in Group II achieved the same sensory level, T5 (2). However, the time to discharge from the recovery room was significantly shorter at 160 (42) minutes ($p<0.01$,t test) in the Group II population. None of the patients enrolled in the study developed PLPC, or neurologic complications. One patient was excluded from Group II secondary to inadequate sacral anesthesia with the initial dose.

Conclusion: To date, there have been no systematic studies evaluating the dose-response of hyperbaric bupivacaine administered via the continuous spinal technique. As demonstrated in this study, continuous spinal anesthesia provides equivalent levels of sensory anesthesia with considerably less anesthetic agent, thus allowing for a more rapid regression of the nerve block and earlier discharge from the recovery area. This makes continuous spinal anesthesia an attractive technique for procedures of indeterminate duration, e.g. TURBT. The data thus far indicates no increase in the incidence of postoperative anesthetic complications. Future studies will further characterize bupivacaine's dose-response curve when administered for continuous subarachnoid anesthesia.

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Title: THE NEED FOR AN ANESTHESIA PREOPERATIVE EVALUATION CENTER

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INTRODUCTION:

Changes in both government reimbursement and third party payers have altered the admission and discharge criteria of hospitalized patients. Nowhere is this more evident than in the elective surgical patient. Six years ago, at the University of California, San Diego Medical Center, a new program was created to admit patients to the hospital on the morning of their surgical procedure. This program was called "Sameday A.M. admits" or SAMA. When the program began it primarily involved medically stable patients coming for minor surgical procedures (e.g. herniorraphies). A review of operating room records revealed that at the time of the program's inception only 9.5% of the surgical patients were eligible to be processed by the SAMA system. By 1987 however, changing criteria swelled this number to more than 25% of our patients (aproximately 285 per month) being admitted through SAMA. Operating room delays because of inadequate patient preoperative evaluations were soon evident. It became clear that we needed a better system of evaluating these patient's anesthetic risk prior to their arrival in the holding area. We therefore recognized the need to open an outpatient facility dedicated to fully evaluating all SAMA patients preoperatively.

METHODS:

We proposed to create our own center to be called the "Anesthesiology Preoperative Evaluation Center" (APEC) whose first mission was to eliminate wasted time in the operating room. We had several long term goals in mind. The first was to decrease the anxiety patients in a large institution or university system feel as a result of it's overwhelming size and beaurocracy. To accomplish this we sought to provide "one stop" service. Here, patients could meet the anesthesiologist, have the appropriate laboratory samples drawn, and receive preoperative teaching by specially trained nursing personnel. Second, we wished to decrease the number of delays in the operating room felt secondary to inadequate screening and preoperative evaluation. Third, we wanted to provide our patients with the highest quality care by having the luxury of time to fully evaluate all problems in an environment outside of the operating room. Lastly, we hoped to improve our rapport with patients and correct any misconceptions they may have about the role of the anesthesiologist during their surgery.

RESULTS:

After convincing the hospital administration about the neccessity of the APEC, we became operational in April, 1988. The center consists of a reception area, two small examination rooms, and a laboratory area where blood samples are drawn and ECGs are done. It is staffed daily (hours 10:30 a.m. to 4:30 p.m.) by two anesthesia residents (usually those with upcoming night call) and a faculty member, as well as secretarial and nursing support. After a patient meets with their surgeon who decides that an operative procedure is needed, an appointment is made to have the patient evaluated in the APEC. Because of the difficulties some patients have with coming back a second time to the hospital, we hold appointment slots for "walk ins" (those who come directly from the surgical clinic.) We also use the facility to coordinate the work up of those patients at "high risk" for either an anesthetic or the surgical procedure. These patients will need further consultations (e.g. cardiology and pulmonary) prior to preoperative clearance. When necessary they may need to return to the APEC.

DISCUSSION:

Over the past year, the APEC has become an integral part of the patient care at our institution. We currently evaluate approximately 300 patients per month, which also includes ambulatory patients ("come and go") who have medically complicated problems. In January through July of 1988, there were 17 first case delays traced to inadequate preoperative evaluation. No data was available on overall delays in the operating room. From July through December of 1988, this number decreased to three, and for the 1989 calendar year only one first case delay has occurred in a patient seen in the APEC. In an operating room running at greater than 90% usage these time delays are critical. This program has also been welcomed by patients who feel that their anesthesia evaluation is important and an integral part of their UCSD experience, and by our surgical colleagues who appreciate the thoroughness of our evaluations. Our current goal is to to expand the facility and incorporate all outpatients. Changes in surgical practice has dictated a change in anesthetic practice. No longer are complicated patients in the hospital the night prior to surgery and we think it is imperitive that all institutions develop a method of adequately evaluating patients preoperatively.

TITLE: **HEMODYNAMIC EFFECTS OF AMRINONE IN PATIENTS RECOVERING FROM AORTOCORONARY BYPASS SURGERY**

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INTRODUCTION: Intravenous amrinone, introduced for acute treatment of congestive heart failure, is now used most commonly to improve cardiac performance in surgical patients following cardiopulmonary bypass (personal communication, Charles Nuttall, Winthrop Pharmaceuticals, New York). Neither amrinone dosing nor the typical responses have been described in a coronary bypass surgical population. Here we compare the hemodynamic effects of increasing doses of amrinone in hemodynamically stable patients following elective aortocoronary bypass grafting.

MATERIALS AND METHODS: Our research protocol was approved by our IRB. Twenty-nine patients with pre-operative left ventricular ejection fraction > 45% gave informed consent to the study. The study took place 24 to 36 hours postoperatively when the patients were extubated, hemodynamically stable, and had received no vasoactive or inotropic agents for the previous two hours. Pulmonary and radial artery catheters (placed preoperatively) were used.

At each measurement point, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and thermodilution cardiac output (the average of 2 to 4 measurements) were recorded.

After baseline measurements were recorded, amrinone was administered in one of three dosing schedules. Low-dose amrinone was administered as a 0.75 mg/kg bolus over 10 minutes, followed by a maintenance infusion of 10 mcg/kg/min. Medium-dose amrinone consisted of a 1.5 mg/kg load followed by a maintenance infusion of 20 mcg/kg/min. High-dose amrinone was infused as a 2.25 mg/kg load, followed by a maintenance rate of 20 mcg/kg/min. Measurements were repeated after the loading dose (10 min), and after 10 min of the infusion (20 min of amrinone).

Data are reported as means ± SEM. Analysis of variance for repeated measures was followed by Dunnett t-test to assess drug effect. $P < 0.05$ was considered significant.

RESULTS: Amrinone increased HR and cardiac index (CI), and reduced PCWP and MAP in a dose-dependent fashion (Table 1). Amrinone at 0.75 mg/kg raised CI 8.5%; 1.5 mg/kg raised CI 11.5%; 2.25 mg/kg raised CI 14.5% (Figure).

DISCUSSION: Our data demonstrate that amrinone increases cardiac performance in patients recovering from coronary artery surgery in a dose-dependent manner. Moreover, only small increases in cardiac output are produced in postoperative patients at an amrinone dose (0.75 mg/kg) which has been reported to be highly efficacious in patients with chronic congestive heart failure. In patients recovering from coronary artery surgery, low-dose amrinone (.75 mg/kg) increases cardiac index roughly equivalent to 10 ng/kg/min epinephrine (1). High-dose amrinone (2.25 mg/kg) has an effect roughly equivalent to 20 ng/kg/min epinephrine (1).

We conclude that standard doses of amrinone which effectively increase cardiac index in patients with chronic congestive heart failure have little effect in patients recovering from coronary bypass surgery who have normal pre-operative left ventricular ejection fractions. However, at higher doses, amrinone consistently increases cardiac index in a dose-dependent manner.

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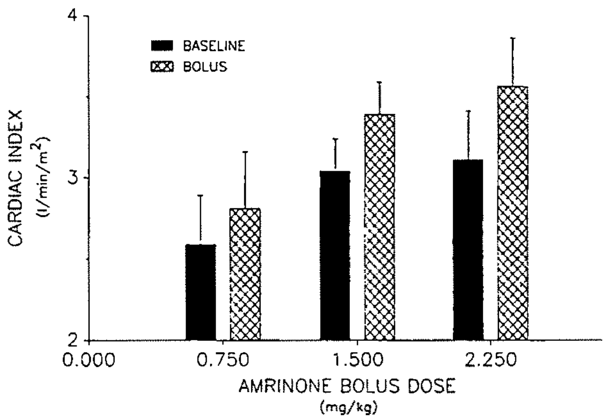
TABLE 1. EFFECT OF AMRINONE UPON HEMODYNAMICS

	Baseline	10 min	20 min
0.75 mg/kg + 10 mcg/kg/hr		**n=6**	
HR	94 ± 6	97 ± 6*	99 ± 6*
MAP	87 ± 2	77 ± 5*	80 ± 2
PCWP	14 ± 1	12 ± 1*	12 ± 1*
CI	2.6 ± .3	2.8 ± .4*	2.8 ± .3*
1.5 mg/kg + 20 mcg/kg/min		**n=14**	
HR	90 ± 3	100 ± 3*	100 ± 4*
MAP	88 ± 3	77 ± 3*	77 ± 3*
PCWP	14 ± 1	12 ± 1*	12 ± 1*
CI	3.0 ± .2	3.5 ± .2*	3.4 ± .2*
2.25 mg/kg + 20 mcg/kg/min		**n=9**	
HR	88 ± 4	99 ± 3*	99 ± 4*
MAP	83 ±74	71 ± 2*	72 ± 3*
PCWP	12 ± 1	8 ± 1*	8 ± 1*
CI	3.1 ± .3	3.5 ± .3*	3.6 ± .3*

* $P < 0.05$ compared to baseline.

MEAN CARDIAC INDEX FOLLOWING AMRINONE BOLUS



Title: Cardiovascular Effects of Desflurane and Nitrous Oxide in Humans

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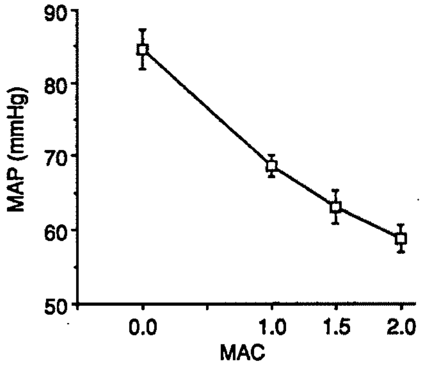
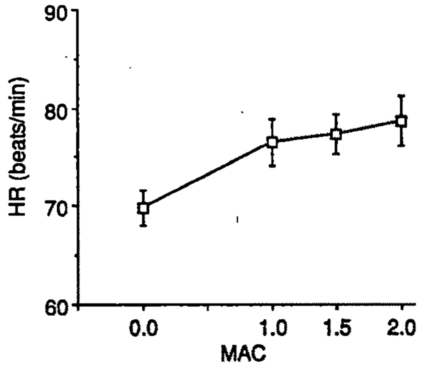
Introduction. Desflurane (I653) is a promising inhalational anesthetic recently approved for experimental use in humans. In swine when administered with nitrous oxide, it has cardiovascular properties indistinguishable from isoflurane. We designed the following experiment to determine the cardiovascular effects of Desflurane and nitrous oxide in humans.

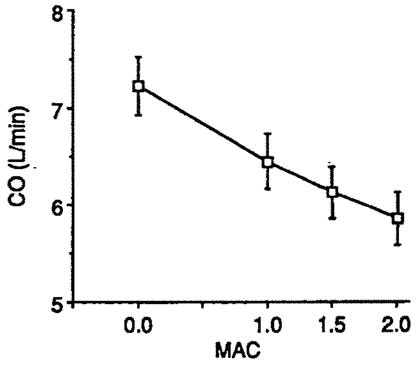
Methods. Following approval of our committee on human research and informed consent, we studied 12 healthy males (ages 20-26) not subjected to surgery or the administration of other drugs. Data were obtained from radial and pulmonary arterial catheters with the subjects awake and anesthetized. In random order, 1, 1.5, and 2.0 MAC anesthesia of desflurane (MAC = 6%) and 60% nitrous oxide (assumed to contribute 0.5 MAC) were evaluated during controlled ventilation and normocarbia. All measurements were recorded at least 10-15 minutes after stabilization of the alveolar concentration of desflurane.

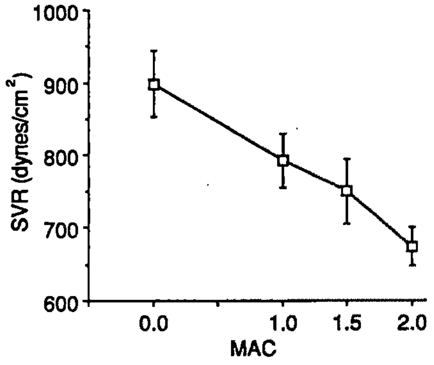
Results. Compared with awake values, right atrial and mean pulmonary artery pressures increased 98 and 47% respectively, and mean arterial pressure (MAP), cardiac output (CO), and systemic vascular resistance (SVR) decreased 19-31% at 2.0 MAC (figures, +/- SEM shown). Heart rate increased 10% at 1 MAC and did not change further. Changes in diastolic pulmonary artery pressures paralleled the changes in right atrial pressures.

Discussion. Like previous experiments with isoflurane and nitrous oxide in human volunteers,[1] our current studies reveal a dose dependent depression of blood pressure and systemic vascular resistance. However in our volunteers, cardiac output also decreased significantly despite the decrease in SVR and increase in filling pressures. These results suggest that although the cardiovascular effects of desflurane-nitrous oxide anesthesia are similar to those of isoflurane-nitrous oxide, desflurane may produce less increase in heart rate but more myocardial depression than isoflurane.









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Title: THE NEUROMUSCULAR EFFECTS OF DESFLURANE (I-653) IN HUMAN VOLUNTEERS

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Introduction. Desflurane (I-653) is a promising new volatile anesthetic currently undergoing clinical trials. It is derived from isoflurane by the substitution of a fluorine atom for a chlorine atom. Its effects on neuromuscular function are unknown. Because of the importance of such effects on the clinical conduct of anesthesia we undertook this study.

Methods. Following approval from our Committee for Human Research 9 ASA physical status I, male volunteers aged 20 to 27 yr were anesthetized by inhalation of desflurane in oxygen. Endotracheal intubation was performed without the aid of muscle relaxants. Esophageal temperature was maintained between 36.5 and 37 °C. Neuromuscular responses were studied at desflurane end-tidal concentrations of 3, 6, 9 and 12%, with and without nitrous oxide, 60%, and during normo, hypo and hypercapnia. End-tidal concentrations of desflurane, and CO_2 and inspired concentrations of nitrous oxide were measured by a Puritan Bennett 254 Airway Gas Monitor modified for desflurane analysis. Neuromuscular function was assessed by measuring the mechanical evoked response of the adductor pollicis muscle to supra-maximal stimulation of the ulnar nerve at the wrist. We used train-of-four (TOF) at 2Hz and tetanus for 5 s at 50, 100 and 200 Hz, each delivered consecutively, at intervals of 15 s. We calculated the ratio of the amplitude of the fourth TOF response in each train to that of the first (TOF ratio) and the decrement in the amplitude of the tetanic responses over 5 s (fade). The relationship of each variable to end-tidal desflurane concentration was determined by linear regression. Results with and without nitrous oxide and at normo, hypo and hypercapnia, were compared by t test or ANOVA. Statistical significance was inferred at $P < 0.05$.

Results. The TOF ratio decreased, and the magnitude of fade of the tetanic response at 50, 100 and 200 Hz increased with increasing concentrations of desflurane (table 1). Neither nitrous oxide nor hypo or hypercapnic states affected neuromuscular responses.

Discussion. Desflurane causes a significant dose-dependent decrease in the TOF ratio and fade of the response to tetanic stimulation. Similar effects have been reported for halothane, isoflurane and enflurane.[1,2] Miller *et al* studied tetanic responses in patients during anesthesia with 1.25 MAC halothane or isoflurane, concentrations which are equivalent to 9% desflurane.* They found that at 120 Hz significant fade occurred in no patients receiving halothane and in 30% of those receiving isoflurane. In our study, at a frequency of 100 Hz, 100% of our subjects showed > 10% fade (table 2). Desflurane, therefore, appears to have greater neuromuscular depressant effects than either halothane or isoflurane. These results suggest that desflurane will be a potent potentiator of the non-depolarizing neuromuscular blocking drugs and that its use in clinical practice will permit reduced doses of these drugs to be used.

Table 1. Neuromuscular Responses (%).

Desflurane conc.	**3%**	**6%**	**9%**	**12%**
TOF ratio	100±2	97±6	95±8	79±23
Fade at 50 Hz	15±9	15±11	24±13	54±22
Fade at 100 Hz	25±13	34±16	72±16	84±22
Fade at 200 Hz	58±25	68±35	83±27	94±11

All values are mean ± SD

Table 2. Percentage of cases in which tetanus was not sustained (fade > 10%).

Desflurane concentration	**3%**	**6%**	**9%**	**12%**
50 Hz tetanus	75	72	89	94
100 Hz tetanus	92	100	100	100
200 Hz tetanus	92	95	100	100

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* Rampil IJ *et al.* (manuscript in preparation)

Title: **EPIDURAL MEPIVACAINE FOR CESAREAN SECTION:EFFECTS OF pH ADJUSTED SOLUTION**

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Introduction: Onset of local anesthetics occurs when a drug enters the nerve axoplasm and attaches itself within the sodium channel of the nerve. The structures the drug must traverse are permeable to the nonionized form and are nonpermeable to the ionized form. Previous studies have reported that elevation of the pH of local anesthetics is associated with augmented quality and duration of the block.[1-2] This is most important because epinephrine containing solutions are commonly acidotic, and the alkalinization of these solutions increases the nonionized form significantly. This study was undertaken to determine the effect of adding sodium bicarbonate to 2% mepivacaine with epinephrine 1:200.000 solution.

Methods: Informed consent was obtained from 70 patients, homogeneous as respect to weight and height, scheduled for repeated elective cesarean section under epidural anesthesia. Institutional approval was also obtained. After an intravenous infusion of 1000 ml of Ringer's lactate solution,an epidural catheter was inserted at L2-L3 level and advanced 2 cm cephalad. The patients were randomly assigned to one of two groups of 35 patients each, to receive either the standard commercial preparation of 2% mepivacaine with epinephrine or the pH adjusted solution. Both the investigator and the patient were blinded to the pH of the solution used. The pH adjusted mepivacaine was freshly prepared by the addition of 0.1 mEq/ml of sodium bicarbonate to the standard mepivacaine solution. This addition resulted in a pH elevation from 4.492 to 7.173 (mean values). Surgical anesthesia to the T4 level was obtained with incremental 5 ml doses. Measurements of sensory and motor block were done at 1-2 minutes interval beginning after the completion of the epidural injection. The onset time was measured as loss of scratch sensation at L1-L2 level.
Time to peak-effect was recorded as the time to sensory loss(pin-prick) at the highest segment reached. The duration of the block was recorded as time to regression by two segments,evidenced by the pin-prick sensation. The motor block was evaluated by Bromage's criteria. All data were subjected to Student's t-test analysis for statistical significance. A p-value less than 0.05 was considered statistically significant.

Results: Raising the pH of the local anesthetic resulted in significant shortening of the time of onset and time of peak-effect(Table 1).
There were no significant differences among the two groups with respect to the duration of the block,the intensity of motor block or the mean dose of mepivacaine used.

No neonatal depression was observed in both groups using Apgar scores,blood gas analysis and ENNS neurobehavioral tests.

Table 1

	mepivacaine	pH adjust.mepivacaine
pH	4.492±0.13	7.173±0.22
onset time(min)*	16±3.2	9±1.8
peak effect(min)*	21±5.1	11±2.04
duration(min)	142±8.3	146±5.2
total dose(mg)	380±21.2	387±18.9

* p <0.01

Discussion: This study confirms previous studies that pH adjusted solutions act more rapidly on nerve fibers than do commercial solutions.[1-2]
The pKa of mepivacaine is 7.7.In this study the pH of mepivacaine pH adjusted solution was 7.30, so that a larger amount of local anesthetic in the unionized form was available. In one study,raising the pH of bupivacaine in cesarean section the time to peak-effect decreased from 24.8 to 18.08 minutes.[3]
The safety of epidural mepivacaine with respect to neonatal outcome has been previously demonstrated[4], and was also confirmed in this study.
The commonly used mepivacaine solutions allow the surgery to proceed after an average time of 20 minutes. Raising the pH of the solution prior to injection,will increase the total amount of base available for neural diffusion. The addition of 0.1 mEq/ml of sodium bicarbonate decreased significantly the onset and the peak effect times,allowing the surgery to proceed more rapidly,that may be of great interest in cesarean section.

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TITLE: ROPIVACAINE VS. BUPIVACAINE: A RANDOMIZED, DOUBLE BLIND, COMPARISON FOR EPIDURAL ANESTHESIA.

AUTHORS: RL Carpenter, MD, DL Brown, MD, GE Thompson, MD

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Introduction: Ropivacaine is an amide local anesthetic structurally related to bupivacaine, yet less cardiotoxic (1). Most animal studies indicate that ropivacaine is less potent than bupivacaine (2). However, the relative potencies of the two drugs have not been compared in humans . Our investigation was designed to compare the clinical effectiveness of ropivacaine and bupivacaine for epidural anesthesia.

Methods: After approval by our Committee on Human Research and informed consent, 45 ASA I or II patients scheduled for lower extremity orthopedic surgery were studied. Premedication consisted of diazepam 5 to 10 mg po, midazolam 1 to 3 mg iv, and/or fentanyl 50 mcg iv. Single dose epidural blocks were performed at L2-3 or L3-4 interspaces, in the lateral decubitus position. A test dose of 3 ml lidocaine 1.5% with epinephrine 5 mcg/ml was injected. Patients were randomly assigned to receive 20 ml of either ropivacaine 0.5% or bupivacaine 0.5%, with no added epinephrine. All investigators were blinded to the identity of the solutions. Sensory anesthesia was assessed by pinprick with a 27 g needle and motor blockade was assessed by the Bromage scale (0=no motor paralysis, 1=inability to raise extended leg, 2=inability to flex knee, 3=inability to flex ankle) at 5, 10, 15, 20, 25, 30 min and thereafter every 15 min until resolution. Quality of anesthesia was judged at the end of surgery as satisfactory or unsatisfactory by the investigator. Differences were assessed by Mann-Whitney U test, ANOVA for repeated measures, and Fischer's exact test.

Results: One patient did not develop an epidural block and was excluded from the data analysis. The remaining 44 patients were evenly divided between the two anesthetics. Adequacy of sensory anesthesia did not differ (21/22 vs 22/22). The onset of sensory analgesia, peak sensory block height, degree of motor blockade, and time until 2-segment regression did not differ (Table 1, Figure 1). Duration until complete resolution of sensory and motor blockade was slightly longer with bupivacaine. Patients were of similar age, height, weight, gender, and ASA status. Finally, no patient had evidence of nerve injury after the epidural anesthetic.

Discussion: Most previous animal studies have indicated that ropivacaine is less potent than bupivacaine. However, we found ropivacaine 0.5% to be as effective for orthopedic surgery as bupivacaine 0.5% and thus, we conclude that the two drugs are clinically equieffective at this concentration. We caution that eqieffective should not be interpreted to mean equipotent. We did not develop a dose response curve, and therefore, did not identify the minimum effective dose (or concentration) for either drug. The volume or concentration of one or both of these drugs could have been greater than necessary. However, our clinical experience indicates 0.5% bupivacaine is the lowest concentration that will provide effective anesthesia for these operations, and we would rarely perform epidural anesthesia with less than 20 cc for this type of surgery. Although, we have little clinical experience with ropivacaine, preliminary results suggest that a concentration of 0.25% would not produce adequate anesthesia for these operations. Finally, ropivacaine, like bupivacaine, produces greater sensory than motor blockade. The minimal motor blockade produced by this concentration indicates that higher concentrations of ropivacaine will be required to produce reliable motor blockade.

Table 1. Comparison of Ropivacaine and Bupivacaine

Characteristic	Ropivacaine	Bupivacaine
Onset to (min)		
T10	11±6	13±11
S5	21±8	20±10
Regression (min)		
2-segment	177±49	181±68
to T10	237±65	257±51
Total Duration (min)		
Sensory Block	333±54*	394±53
Motor Block	220±52*	276±52
Peak		
Block Height	T5±2	T5±3
Bromage Score	1±1	1±1

*p<.05 (Mann-Whitney U) Data are means ± SD.

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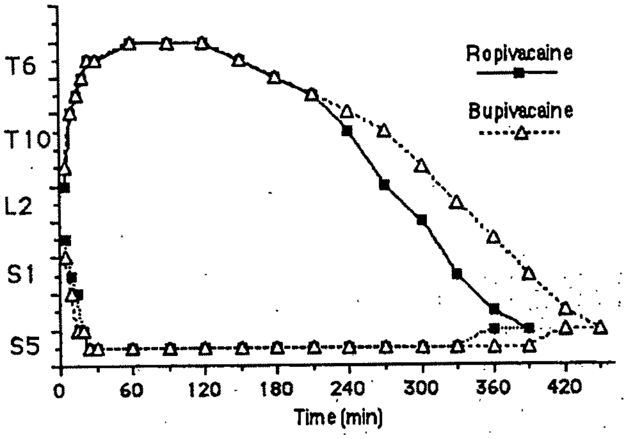
Figure 1. Distribution of sensory anesthesia vs time.



TITLE: SPINAL ANESTHESIA: WHO IS AT RISK?

AUTHORS: RL Carpenter MD, RA Caplan MD, DL Brown MD, B Nadir RN RRT

AFFILIATION: Virginia Mason Medical Center, Seattle, Washington

INTRODUCTION: Recent reports of cardiac arrest during spinal anesthesia has caused us to re-evaluate the incidence of hemodynamic alterations during spinal anesthesia (1). We wondered if certain patient characteristics or anesthetic techniques were associated with an increased risk. To address these questions we began collecting data on 1000 consecutive spinal anesthetics. This abstract outlines the initial 229 patients in our study.

MATERIALS AND METHODS: After approval by our Institutional Review Board, we prospectively studied 229 patients who received spinal anesthesia. We recorded characteristics of 1) the patient: Ht, Wt, age, gender, ASA physical status, medications, and medical history; 2) the spinal technique: premedication, sedation level (1=wide awake, 2=drowsy, 3=dozing intermittently, 4=mostly sleeping, 5=only awakens when aroused, 6=unarousable), IV fluids, drug, dose, baricity, vasoconstrictors, and block height; 3) patient physiology: BP, HR, RR, and SpO2; and 4) the location of surgery. Measurement of patient physiology, sedation levels, and block levels were recorded every 15 min for one hour after the spinal anesthetic was performed. These measurements were also recorded if the patients developed bradycardia, hypotension, or dysrhythmias. Bradycardia was defined as a HR < 50 bpm. Hypotension was defined as a systolic BP < 90 mmHg. Differences in characteristics were assessed by ANOVA, Chi Square, and Fishers Exact Test.

RESULTS: 35 (15.3%) of patients developed bradycardia, occurring 50 ± 43 (mean ± SD) (range 1 to 204) min after initiating spinal anesthesia. Patients who developed bradycardia were more likely to be ASA I or II, to be undergoing a pelvic or inguinal operation, and to have received hyperbaric solutions (Table 1). 102 patients (44.5%) developed hypotension, occurring 27 ± 24 (range 2 to 120) min after initiating spinal anesthesia. Patients who developed hypotension were less likely to have received lidocaine and more likely to have received tetracaine. Hypotension occurred more frequently during intra-abdominal surgery. 30 min after initiating spinal anesthesia, patients who became hypotensive had higher block heights, were more sedated, and had received less IV fluids (Table 2). 4 patients (2%) had dysrhythmias during spinal anesthesia. We could identify no distinguishing characteristics. No other factors were associated with these hemodynamic perturbations. Finally, no patient developed cardiac arrest.

DISCUSSION: Traditionally, spinal anesthesia has been considered safer than general anesthesia. However, recent reports suggest that cardiac arrest, death, and severe morbidity can occur during spinal anesthesia in relatively healthy patients, even when vigilance appears to be appropriate (1). We have identified two cardiovascular side-effects, bradycardia and hypotension, that occur commonly in healthy patients and appear to be associated with characteristics identified in Tables 1 and 2. We caution that these are preliminary associations and do not prove a cause-effect relationship. However, appreciation of these characteristics may help identify those with altered risks.

Table 1. Characteristics associated with Bradycardia (Brady).

	Brady			
Characteristic	Yes	No	%Brady	P
ASA:				
1	9	36	20	.04
2	25	120	17	
3	1	39	3	
Baricity:				
Hyperbaric	34	175	16	.02
Hypobaric	1	13	7	
Isobaric	0	6	0	
Surg Location:				
Lower Extrem	9	82	10	.04
Pelvic/Ing	25	89	22	
Intra-abdom	1	22	4	

Table 2. Characteristics associated with Hypotension (Hypo).

	Hypo			
Characteristic	Yes	No	%Hypo	P
Drug:				
Lidocaine	20	37	14	.01
Tetracaine	61	48	56	
Bupivacaine	15	31	33	
Procaine	6	11	35	
Surg Location:				
Lower Extrem	31	60	34	.0001
Pelvic/Ing	9	105	8	
Intra-abdom	22	2	92	
30 min p̄ Block				
Block Ht	T5±3	T6±3		.001
IV Fluids(cc)	970±340	1118±375		.003
Sedation	3.4±1	2.7±1		.0004

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TITLE: GLYCOPYRROLATE DOES NOT PREVENT BRADYCARDIA DURING SPINAL ANESTHESIA

AUTHORS: R.L. Carpenter, M.D. and D.C. Mackey, M.D.

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INTRODUCTION: Bradycardia, hypotension, and nausea and/or vomiting (N/V) are adverse effects known to occur during spinal anesthesia[1]. Glycopyrrolate premedication (iv) prevents bradycardia during general anesthesia[2] and produces minimal change in heart rate[3]. We hypothesized that glycopyrrolate might reduce the incidence of bradycardia, hypotension, or N/V during spinal anesthesia, without producing tachycardia.

MATERIALS AND METHODS: After approval by our Committee on Human Research, seventy-three patients, undergoing spinal anesthesia, were randomized to receive either glycopyrrolate or normal saline iv immediately after administration of spinal anesthesia. The study was divided into two parts; Group 1 (n=40) patients received either glycopyrrolate 0.2 mg or saline 1.0 ml, Group 2 (n=33) patients received either glycopyrrolate 0.4 mg or saline 2.0 ml. The attending anesthetist was blinded as to the solution administered. Heart rate (HR) and blood pressure (BP) were recorded at baseline, 5, 10, and 15 min post block. Anesthetic level was determined by pinprick 15 min post block. Episodes of bradycardia (HR less than 60, hypotension (>25% decrease in BP), and (N/V) were recorded. Treatment was determined by the attending anesthetist.

RESULTS: There was no significant difference in age, height, weight, or block height in those subjects receiving glycopyrrolate 0.2 mg, glycopyrrolate 0.4 mg, or saline. The average block height was $T_6 \pm 3$ dermatomes (mean ± SD). Patients in both groups experienced significant adverse effects (Group 1 = 42.5%, Group 2 = 45%) (Table I). Glycopyrrolate administration (0.2 or 0.4 mg) did not decreased the incidence of adverse effects. The glycopyrrolate 0.4 mg study was terminated when 2 patients developed significant tachycardia. The incidence of adverse effects in saline controls (n=35) was: bradycardia 9%, hypotension 37%, and N/V 6%.

TABLE I. Influence of gylcopyrrolate (G) on adverse effects during spinal anesthesia

	n	HR	BP	N/V
Group 1				
G (0.2mg)	20	↓4	↓4	2
Saline	20	2	8	1
Group 2				
G (0.4)	18	2	6	1
Saline	15	1	5	1

DISCUSSION: Glycopyrrolate (0.2-0.4 mg) was ineffective for preventing adverse effects that occur commonly during spinal anesthesia. Our results indicate that glycopyrrolate 0.4 mg may have a greater potential for harm than good when used prophylactically during spinal anesthesia. Sudden asystole during spinal anesthesia has recently been described as a cause of morbidity and mortality in healthy patients. Although our study is too small to assess the efficacy of glycopyrrolate for preventing sudden cardiac arrest, it seems unlikely that glycopyrrolate would prevent aystole when it is ineffective for preventing bradycardia.

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TITLE: COMPARISON OF ALFENTANIL AND HALOTHANE FOR PEDIATRIC ENT SURGERY

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Alfentanil is a synthetic opioid analgesic with a rapid onset and short duration of action. This study compares the effects of alfentanil (AL) or Halothane (HA) on recovery and postoperative pain in pediatric outpatients undergoing adenoidectomy.

METHODS:

Institutional approval and informed consent were obtained to study 40 ASA PS I or II 2-10 year old unpremedicated children undergoing adenoidectomy. Anesthesia was induced with either N_2O/O_2/Halothane administered via face mask, or intravenous surital 5 mg/kg based on the child's preference and acceptance. This was followed by iv vecuronium 0.1 mg/kg to facilitate tracheal intubation. Patients were randomized to one of two study groups using a sealed envelope technique following induction of anesthesia. In group I patients, anesthesia was maintained with halothane N_2O and oxygen. The inspired concentration of halothane was adjusted between 0.5% and 1.5% to maintain blood pressure within 20% of control values. Patients in Group II had their halothane discontinued following tracheal intubation and received 50 mcg/kg bolus of alfentanil followed by an alfentanil infusion at a rate of 0.5-3.0 mcg/kg/min. The infusion rate was adjusted to maintain BP within 20% of control values. Atropine 0.01 mg/kg was administered I.V. to any patient if heart rate decreased to 20% below baseline value.

Following completion of surgery halothane or alfentanil were discontinued, and neuromuscular blockade was reversed by i.v. neostigmine 0.06 mg/kg and atropine 0.02 mg/kg. The N_2O was then discontinued and the times to extubation and awakening were recorded. Upon arrival in postanesthetic recovery room (PARR). Pain was assessed using an Objective Pain Scale (1) and rate of recovery was assessed using Steward's recovery score (2). Patients were assessed every 5 minutes by a research associate blinded to the anesthetic technique used. Intravenous fentanyl 1 mcg/kg was administered to any patient who achieved a pain score of 6 or more on 2 consecutive observations. The discharge time from hospital and the incidence of nausea and vomiting were also assessed. Data were compared among the two groups utilizing Student's t-test and Pearson's chi square or Fisher's exact test.

RESULTS:

Patients in both groups were comparable with regards to age, weight, and duration of both surgery and anesthesia (table 1). The times to extubation and discharge were similar in both groups (table 1). Pain scores, analgesic requirements and recovery scores were similar in both groups (table 1). There was no significant differences in O_2 saturation or in the incidence of vomiting between both groups.

Variable	Halothane(HA) (n = 20)	Alfentanil(AL) (n = 20)	
Age (yrs)	3.2 ± 1.0	3.6 ± 1.2	NS
Wt (kg)	15.7 ± 2.2	17.4 ±5.2	NS
Anes Dur (mins)	47.6 ± 7.1	50.2 ± 14.0	NS
Surg Dur (mins)	23.1 ± 9.1	25.6 ± 12.0	NS
Awake (mins)	8.9 ± 3.2	7.0 ± 3.8	NS
Recovery (mins)	8.1 ± 7.2	12.8 ± 12.4	NS
Discharge (mins)	123.7 ± 40.2	139.9 ± 57.9	NS
Pain Score in PARR			
0	3.9 ± 2.9	3.2 ± 2.8	NS
5 minutes	4.5 ± 2.8	2.9 ± 2.5	NS
Lowest SpO_2	91.8 ± 3.7	90.9 ± 6.7	NS
Fentanyl required	*5(25%)	*2(10%)	NS
Atropine required	*4(20%)	*6(30%)	NS
Vomiting	*4(20%)	*9(45%)	NS

* Number of Patients
NS = Not Statistically Significant

DISCUSSION:

Anesthesia for ambulatory surgery should allow patients to recover rapidly from anesthesia, be relatively pain free, and have minimal side effects. This allows rapid discharge of patients from hospital. Although patients was received alfentanil tended to have lower pain scores, required less postoperative analgesia and had a higher incidence of vomiting, when compared to the group II patients who received halothane, these differences were not statistically significant. Alfentanil's short duration of action is due to its rapid redistribution to other tissues and its short elimination half life. This study demonstrated that alfentanil is a suitable anesthetic for ambulatory surgery in children and does not prolong recovery and discharge time when compared to halothane.

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Title: **VENTILATORY EFFECTS OF SUBARACHNOID FENTANYL IN THE ELDERLY**

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Introduction: Subarachnoid fentanyl has been shown to improve,in different doses,both intraoperative and postoperative analgesia.[1,2] Mild side effects were noted,mostly pruritus.No changes in respiratory rate, even in high doses[2] or clinical respiratory depression have been reported in the elderly patients.[3] This randomized,dose-response,double blind study was undertaken to evaluate the ventilatory effects of different doses of subarachnoid fentanyl in the elderly patient.

Methods: Twentyeight male patients scheduled for elective urologic surgery were studied.The study protocol received the approval of the Ethics Committee.Informed consent was obtained from all patients.The patients were randomized to receive subarachnoid hyperbaric bupivacaine 15 mg with the addition of 50,25 or 12.5 μg of fentanyl(groups A,B and C respectively)or 1 ml of saline(group D,controls)for a total of 4 ml. Ventilatory measurements were performed in all subjects while resting in a supine 30 degrees head-up position,before(baseline value)and 90,150 and 480 min after the subarachnoid injection.Were evaluated the following:respiratory rate(RR),minute ventilation(VE), respiratory drive,respiratory timing and the ventilatory response to CO2,with the Read's rebreathing method.Respiratory drive and respiratory timing were calculated from the tidal volume trace by maximum inspiratory flow(Vt/Ti)and inspiratory time/total breathing time ratio(Ti/Ttot)respectively.Heart rate,arterial blood pressure and respiratory rate were noted every 2 h.All patients were monitorized by pulse oximetry and transcutaneous O2/CO2 continuous monitoring intraoperatively and for 120 min postoperatively. Postoperative analgesia was measured as time to the first patient's request of analgesics.All patients were observed and asked for the presence or the absence of nausea,vomiting,pruritus and drowsiness. Statistical analysis was performed by ANOVA and Student's Newman Keultz test when appropriate.

Results: There were no significant differences between the groups as respect to age,weight and height.No significant differences in vital signs,O2 saturation and O2/CO2 transcutaneous monitoring were observed. No significant changes in RR,VE,Vt/Ti,Ti/Ttot and PETCO2 values were observed in any of the groups. In groups C and D the slope VE/PETCO2 did not change from baseline values.Apnea and periodic breathing were observed in two patients who received 50 g of subarachnoid fentanyl.In group A the slope VE/PETCO2 was significantly below baseline values at 90 and 150 min($p < 0.05$).Mild pruritus and sedation occurred in 5 patients of group A(71.4%)and in 4 patients of group B(57.1%). Nausea and vomiting occurred in the same 2 patients(28%)of group A who had periodic breathing. In group B nause and vomiting were observed in 2 patients(28%). Patients who received the 50 and the 25 μg dose had a prolonged postoperative analgesia as respect to the other two groups(278±38 and 220±41 min versus 178±27 and 125±32 respectively).

Discussion: The intensity and the duration of the respiratory depression observed may be correlated to the concentration of the drug in the CSF. Patients receiving subarachnoid fentanyl 50 μg,had a prolonged postoperative analgesia,but had also a respiratory depression,as shown by the depressed response to the CO2 stimulation test. Subarachnoid fentanyl at the dose of 25 μg seems to be the only dose having significant analgesic affects without a respiratory depression. The potential risk of respiratory depression must be always taken in consideration when intraspinal narcotics are used and a careful monitoring, especially in the elderly,is a key to their safe use as postoperative analgesics.

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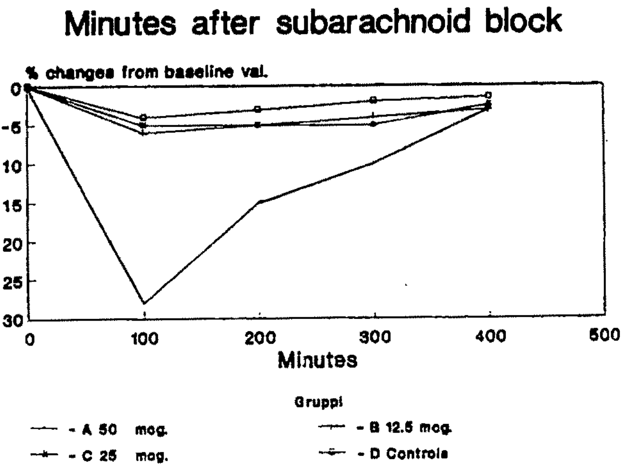

TITLE: INTUBATION WITH OR WITHOUT NEUROMUSCULAR BLOCKADE IN TRAUMA PATIENTS WITH CERVICAL SPINE INJURY

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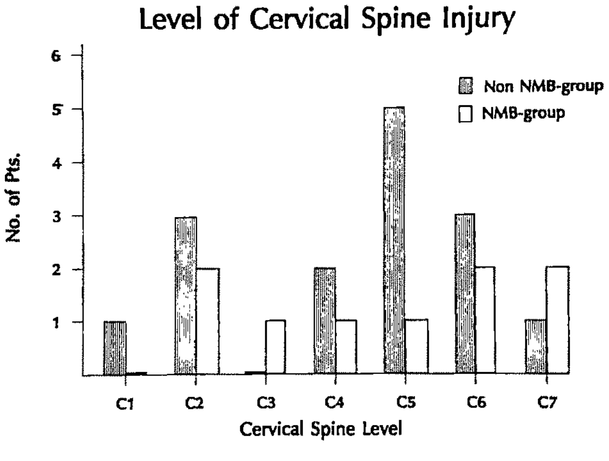
INTRODUCTION: Awake laryngoscopy or nasal intubation are frequently considered the techniques of choice for endotracheal intubation of the patient with cervical spine injury. Arguments against the use of neuromuscular relaxants include the risk of inability to secure the airway, and the risk of excessive cervical spine movement. However, for emergent intubation of patients with multiple trauma including cervical spine injury, there are advantages associated with the use of muscle relaxants. These include control of the combative patient, prevention of increased intracranial pressure, and prevention of patient movement which may worsen cervical spine injury. There have been no quantitative studies to compare the outcomes of emergently performed relaxant facilitated vs. non-relaxant intubation techniques in cervical spine injured patients. This study reviews the experience with such patients at one major trauma center over a four year period.

METHODS: Human Investigation Committee approval for this retrospective study was obtained. Patient records were identified from the trauma registry at Allegheny General Hospital. Patients who suffered a radiographically confirmed traumatic cervical spine injury, and who were emergently intubated within our institution (not in the field) were included. Data was abstracted from all patients who met this criteria during the period 1984 to 1988. Information collected included population data (sex, age, heigth, weight) and injury data. Injury data included description of cervical spine injury, Glasgow Coma Score (GCS), Trauma Score (TS), neurological deficit before and after intubation, and duration of hospital stay. Information pertaining to the intubation for each patient included specific technique, relaxant use, intubation complications, and need for emergency tracheostomy due to failed intubation. Mortality was also noted. For purposes of comparison, patients were classified into two groups: 1) those receiving neuromuscular blockers (NMB group), and 2) those intubated without neuromuscular blockers (non-NMB group). Comparisons between groups were performed using a two-tailed t-test, with statistical significance accepted at $p<0.05$.

RESULTS: A total of 16 patients met the criteria outlined. Of these patients, 7 were intubated using muscle relaxants (NMB group), and 9 were intubated without muscle relaxants (non-NMB group). Comparison of data showed no significant difference in age, weight, or sex distribution between the groups. The mean Glasgow Coma Score (GCS) for the NMB group was 13.7 (SD - 0.75), while for the non-NMB group mean GCS was 9.4 (SD - 4.4). This difference is statistically significant. There was no significant difference between the Trauma Scores (TS) or duration of hospital stay between the groups. There was one fatality in each group. The histogram shown below indicates the anatomic levels of cervical spine injuries in the two groups. Four patients in the NMB group had a spinal cord deficit on arrival, while all 9 patients in the non-NMB group had such a deficit. In all patients, there were no intubation related complications, and no surgical airway maneuvers were required.

DISCUSSION: Frequently trauma patients who require emergency intubation must be treated as if they have cervical spine injuries until such injuries are conclusively ruled out. Many of these patients may require the use of neuromuscular relaxants to facilitate intubation. The degree of morbidity associated with emergency intubation in patients with actual cervical spine injury is unknown. Awake intubation is advocated as a safe means of endotracheal intubation in such patients, but is frequently unsuitable for emergency intubation in the unstable patient with multiple injuries, or the combative trauma patient. We find that neuromuscular blockade to facilitate intubation, in conjunction with head and spine immobilization, is frequently necessary under these circumstances. Review of all cases at our hospital over the most recent four year period shows no cases of change in neurological status in those patients requiring emergency intubation while suffering from cervical spine injury. Those who received neuromuscular relaxants had a significantly higher GCS, which might be associated with an increased degree of patient confusion and/or combativeness. In comparison, patients in the non-NMB group tended to be more stuporous or comatose. NMB use was also determined by factors such as presence of other injuries. This data tends to confirm our belief that appropriate use of NMB, along with careful intubation technique including head and spine immobilization, does provide a safe and reliable technique for emergency intubation of the cervical spine injured trauma patient.



Title : COMPARISON OF BODY HEIGHT AND VERTEBRAL COLUMN LENGTH IN THE TERM PREGNANT WOMEN

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Introduction. Spinal anesthesia is frequently used in the pregnant women for cesarean sections. The common belief is that the spread of spinal anesthesia is related to the body height (1), especially in patients with extremes of body height (2). However, this concept was challenged by some recent studies. Those studies showed that the spread of spinal anesthesia is not related to the body height (3), but is related to the vertebral column length (4).

Our study is aimed to evaluaate the relationship between the body height and the vertebral column length in the term pregnant women, including those with extremes of body height.

Method. After institutional approval and patient consent, 108 term pregnant women were included in our study. They were divided into three groups according to their body heights. Group I (n=23) included parturients with body height equal to or less than 60 inches. Group II (n=68) included parturients with body height between 60 and 65 inches . Grouop III (n=17) included parturients with body height more than 65 inches. Each patient was measured for the body height and the vertebral column length (between C7 prominence and sacral hiatus) when she was in the right lateral decubitus position. The parturients who had vertebral abnormality were excluded. The results of each group were analysed by linear regression analysis to correlate the body height and the vertebral column length. $p < 0.05$ would be considered as statistical significance. Then, the vertebral column lengths were compared between each two groups by using unpaired student's t-test to determine whether there is significant difference of the vertebral column length among these three groups.

Results. There were no significant differences among these three groups with respect to age and body weight . The correlation between the body height and the vertebral column length is shown in the table.

	Body Height (in.) (Mean ± S.E.)	Vertebral Length (in.) (Mean ± S.E.)	r	p
Gr. I (range)	58.8 ± 0.3 (54-60)	20.9 ± 0.8 (18.5-24)	0.37	> 0.05
Gr. II (range)	63.1 ± 0.2 (60.5-65)	22.0 ± 0.3 (19-24)	0.16	> 0.05
Gr. III (range)	66.7 ± 0.3 (65.5-69)	22.4 ± 0.4 (20-24)	-0.28	> 0.05

No statistical significant difference of the vertebral column length among the three groups was found.

Discussion. Since there is a correlation between the vertebral column length and the spread of spinal anesthesia , and our study showed there is no statistical significant correlation between the body height and the vertebral solumn length in all the parturients including those with wide range in body height (54 inches to 69 inches). We believe there is no reason to consider body height as an influencing factor of spinal anesthesia spread.

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TITLE: IS REGIONAL BETTER THAN GENERAL ANESTHESIA FOR CERVICAL CERCLAGE? 9 YEARS EXPERIENCE

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INTRODUCTION: Cervical cerclage is performed for cervical incompetence. Controversial issues include whether this places the pregnant women at an increased risk for premature labor and spontaneous abortion, and the fetus for drug-related teratogenicity. The incidence of fetal loss is increased in this population, and inhalational anesthetics have been implicated by animal studies (1), although retrospective reviews of human experience disagree (2-4). A recent review of 375 cases of cervical cerclage with general anesthesia suggested that the incidence of inevitable abortion (Ab) and low birth weight (LBW) babies was not affected by the type of anesthesia chosen (5). The contribution of type of anesthesia to the patient's coughing on the endotracheal tube or to the degree of uterine relaxation have been debated.

METHODS: After human studies approval, retrospective chart review was performed for all patients undergoing cervical cerclage for the period from 1/79-12/87. 272 patients were identified. The information recorded for each patient included: age, weight, ASA physical status, elective/emergent cerclage placement, fetal gestational age at cerclage placement, gravida/para/abortion, maternal diethyl stilbesterol exposure, birth gestational age, neonatal sex/weight and the type of anesthesia.

RESULTS: The first group (Group A), included abortions, stillbirths and neonatal deaths. In the second group (Group B), LBW was defined as ≤ 2500 g. In the third group were all the remaining infants (Group C). For the patients receiving regional anesthesia, there was one patient in Group A, seven patients in Group B, and 14 patients in Group C. For the patients receiving general anesthesia, there were 29 patients in Group A, 55 patients in Group B, and 166 patients in Group C (Table). When poor outcome is defined as all fetal and neonatal deaths as well as the LBW infants, the incidence of poor outcome with regional anesthesia was 8 of 22 patients (36%) and with general anesthesia was 85 of 250 patients (34%). Chi-square analysis comparing the three outcomes for regional vs general anesthesia showed that there was no significant difference related to type of anesthesia ($p > 0.100$). For the number of patients studied, a power analysis revealed an 80% chance of detecting a 6.5% difference between the regional vs. GA patients ($\delta = 0.0114$; $\sigma = 0.0236$).

DISCUSSION: Since poor outcome of pregnancy occurred in 36% of patients receiving regional anesthesia and in 34% of the patients receiving general anesthesia, these data do not support the choice of one type of anesthesia over another. We conclude that regional anesthesia is as appropriate for cervical cerclage as general anesthesia.

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	Outcome of Pregnancy (Number of Patients)		
Type of Anesthesia	Group A	Group B	Group C
Regional	1	7	14
General	29	55	166

TITLE: MECHANISM OF INHIBITION OF HYPOXIC PULMONARY VASOCONSTRICTION (HPV) BY DOPAMINE VS ISOPROTERENOL

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INTRODUCTION: Dopamine's effect on HPV is controversial. Several investigators have reported dopamine to be a pulmonary vasoconstrictor (1-3) and, while others have reported dopamine to produce no change or augmented HPV (4). Isoproterenol is a pulmonary vasodilator (2). A computer simulation of the pulmonary circulation based on detailed morphologic and biodynamic characteristics of the lung (5,6) allows predictions of blood flow distribution and pulmonary artery pressure (PAP) for comparison with experimental measurements when the conditions for 2 lung compartments (e.g. a hypoxic lobe or lung vs the rest of the lung) are known.

METHODS: For the computer simulation, the data for PAP, CO, left atrial pressure (LAP), and PvO_2 were reported (7). Percent left lung blood flow (%Q_L) and PAO_2 (8) were estimated. Alveolar end-expiratory pressures (Palv) were estimated at 0 cmH_2O and pleural pressure (Ppl) at -2.0 cmH_2O since the dogs chest was closed. These conditions determine the vascular tone and the program then calculates sequentially the diameter and pressure drop across all 22 orders of arteries and veins and of the capillary sheet to arrive iteratively at the unique blood flow distribution at which the resulting PAP are equal for both regions. The amount of constriction is calculated as the ratio of the diameter of the vessel constricted to the diameter relaxed when the transmural pressure is zero. A constriction ratio (CR) of 0.6 corresponds to maximal hypoxic constriction and of 1.0 to no constriction.

RESULTS: When both lungs received 100%-no drug (star), the relative blood flow for the right lung (RQ_R) and left lung (RQ_L) is 0.99 or 1.0 (Figure). When the left lung receives hypoxia-no drug (circles), the left lung vasoconstricts and blood flow is diverted to the right lung. Using hypoxia-no low dose dopamine as an example, this left lung vasoconstriction is shown by the constriction ratio change from 0.99 to 0.76; blood flow diversion is shown by the RQ_L decrease from 1.0 to 0.68. At the same time the 100% O_2 ventilated right lung does not experience any vasoconstriction so that the constriction ratio remains at 0.99; since the hyperoxic lung accommodated the blood diverted to it, the RQ_R increased from 1.0 to 1.17. Upon addition of drugs (squares), e.g., low dose dopamine (2.5 µg/kg/min), there is minimal left lung vasoconstriction as evidenced by the constriction ratio change from 0.76 to 0.70 and there is minimal blood flow diversion as represented by the RQ_L change from 0.68 to 0.64. There is minimal vasoconstriction of the 100% O_2 ventilated right lung as represented by the constriction ratio change from 0.99 to 0.90; the blood flow to the hyperoxic lung is minimally altered as shown by the RQ_R change from 1.17 to 1.13. With high dose dopamine (25 µg/kg/min) both lungs start at a higher relative cardiac output (1.44). The decrease in left lung vasoconstriction is seen by the constriction ratio increase from 0.68 to 0.79 and the decrease in blood flow diversion is seen by the RQ_L increase from 0.64 to 1.31. However, high dose dopamine also caused vasoconstriction of the 100% O_2 ventilated right lung where the constriction ratio decreases from 0.99 to 0.85; the increase in blood flow to the right lung is represented by the RQ_R increase from 1.47 to 1.58. With isoproterenol (0.25 µg/kg/ml), left lung vasodilation is exemplified by the constriction ratio increase from 0.58 to 0.87 and the decrease in blood flow diversion is illustrated by the RQ_L increase from 0.48 to 1.44. Isoproterenol also caused vasodilation of the 100% O_2 ventilated right lung where the constriction ratio increases from 0.81 to 1.0; the increase in blood flow to the right lung is represented by the RQ_R increase from 1.23 to 1.79.

DISCUSSION: The computer model confirms that: (a) the effect of dopamine on HPV is dose-dependent; (b) the effect of high-dose dopamine on the pulmonary vasculature is not simple, but is a combination of vasodilation in areas of high tone (hypoxic lung) and vasoconstriction in areas of low tone (hyperoxic lung); (c) isoproterenol is a pulmonary vasodilator.

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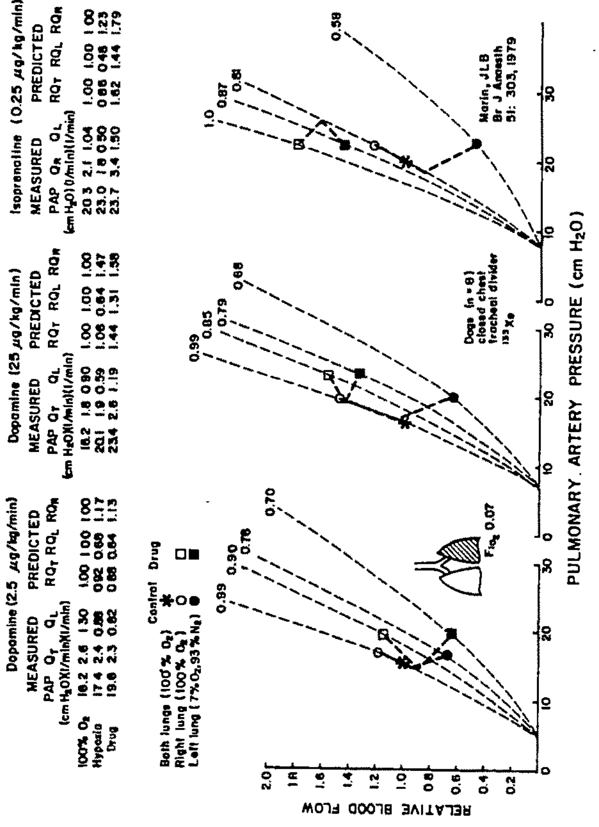
Supported in part by NIH GM29628 and GM07612.



Dopamine (2.5 µg/kg/min)

	MEASURED			PREDICTED		
	PAP (cm H_2O)	Q_T (l/min)	Q_L (l/min)	RQ_T	RQ_L	RQ_R
100% O_2	16.2	2.6	1.30	1.00	1.00	1.00
Hypoxia	17.4	2.4	0.88	0.92	0.68	1.17
Drug	19.6	2.3	0.82	0.88	0.64	1.13

Dopamine (25 µg/kg/min)

MEASURED			PREDICTED		
PAP (cm H_2O)	Q_T (l/min)	Q_L (l/min)	RQ_T	RQ_L	RQ_R
18.2	1.8	0.90	1.00	1.00	1.00
20.1	1.9	0.59	1.06	0.64	1.47
23.4	2.6	1.19	1.44	1.31	1.58

Isoprenaline (0.25 µg/kg/min)

MEASURED			PREDICTED		
PAP (cm H_2O)	Q_R (l/min)	Q_L (l/min)	RQ_T	RQ_L	RQ_R
20.3	2.1	1.04	1.00	1.00	1.00
23.0	1.8	0.50	0.86	0.48	1.23
23.7	3.4	1.50	1.62	1.44	1.79

	Control	Drug
Both lungs (100% O_2)	*	
Right lung (100% O_2)	○	□
Left lung (7% O_2, 93% N_2)	●	■

Title:

DOSE-RESPONSE RELATIONSHIP OF ISOFLURANE VERSUS HALOTHANE ON CORONARY PERFUSION PRESSURE AND FLOW REDISTRIBUTION IN A SWINE MODEL OF CHRONIC CORONARY OCCLUSION

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Introduction: Isoflurane has been suggested to be dangerous in patients with known coronary artery disease, because it may cause coronary vasodilation leading to "steal".[1] We propose to study the hypothesis that redistribution of blood flow away from a collateral dependent zone of the heart will be more dependent on coronary perfusion pressure (CPP) than on the specific inhalational agent (Isoflurane or halothane) being used. A swine model of chronic coronary occlusion is used because this is similar to the human coronary system which lacks native collaterals but can develop disease related collaterals.

Methods: Following approval by the Animal Care and Use Committee of the University of Iowa. Pigs between 7-9 kg were anesthetized with halothane, intubated, and mechanically ventilated. Via a left thoracotomy the left anterior descending coronary artery (LAD) was dissected and a non-occlusion band was placed around it. The pericardium and chest were closed and intercostal nerve blocks were performed with bupivacaine for 12-24 hour analgesia during recovery. After eight weeks, a region of collateral dependent myocardium was developed as they grew into the LAD band. The pigs (approx. 40 kg) were randomly anesthetized with either halothane or isoflurane as the experimental agent and oxygen. After tracheotomy and controlled ventilation on succinylcholine drip, a left femoral arterial line and right internal jugular venous PA catheter were monitored. A median sternotomy and pericardial cradle was established. The constriction band on the LAD coronary artery was identified and ligature was placed around it to assure total occlusion. A Millar Catheter was inserted into the left ventricle via the apex for pressure and dP/dT determinations. The concentration of isoflurane or halothane was adjusted to obtain the pre- determined, randomly selected CPP (DAP-LVEDP) at 30, 40, 45, and 55 mm Hg. After five minutes at each CPP, 2×10^6 radiolabelled microspheres (15 μm diameter) were injected via the left atrial catheter for regional myocardial blood flow determination. Reference samples were simultaneously withdrawn from the right carotid and left femoral arterial lines, beginning 15 seconds prior to microsphere injection at a rate of 2.00 ml/min. for 120 seconds. At the end of all four CPP measurements, KCL was injected into the LA line assuring adequate euthanasia. After removing the heart, the collateral dependent zone was identified by infusing triphenyl tetrazolium chloride in the LAD distal to the occlusion and simultaneously, the normal perfused zone was identified by infusing Evans blue dye in the proximal left circumflex artery. Tissues from each zone were divided into epi-, mid-, and subendocardial regions for blood flow determinations from each isotope counting. Statistical analysis was done by analysis of variance for repeated measures followed by t-test with Bonferroni's correction.

Results: Eight animals were studied in each group. With decreasing CPP of 55 to 30 mm Hg, the end tidal concentration of isoflurane increased from 0.8±0.24% to 2.08±0.28% whereas halothane increased from 0.62±0.12% to 1.4±0.14%. HR, MBP, CVP, PCWP, LVEDP and cardiac output were not significantly different in both groups. $PaCO_2$ was maintained at about 40 mm Hg. There was a significant decrease in regional blood flow at CPP 55 to 30 mm Hg in all myocardial layers for both groups. No intercoronary or transmural redistribution of blood flow was found in either group with decreasing CPP (Table). However, the collateral dependent zone (CD) to control zone (CNT) blood flow ratio was consistently higher in the halothane group.

Table (Mean±SEM)

CPP (mm Hg)	55	45	40	30
CD/CNT SE				
I	0.84±0.10	0.84±0.13	1.01±0.07	0.89±0.12
H	0.94±0.15	0.92±0.14	0.88±0.09	0.98±0.13
CD/CNT EPI				
I	0.88±0.12	0.82±0.09	1.07±0.07	0.94±0.10
H	1.38±0.33	1.28±0.281	1.29±0.31	1.19±0.20
SE/EPI CD				
I	0.86±0.06	0.89±0.06	0.80±0.06	0.77±0.07
H	0.77±0.15	0.84±0.15	0.80±0.12	0.84±0.16
SE/EPI CNT				
I	0.89±0.06	0.89±0.06	0.86±0.08	0.89±0.10
H	0.93±0.09	0.97±0.09	0.95±0.07	0.87±0.07

CD = collateral dependent zone blood flow
CNT = control zone blood flow
SE = subendocardial layer
EPI = epicardial layer
I = isoflurane group (n=8)
H = halothane group (n=8)

Discussion: Our data demonstrates that when isoflurane or halothane was used as the sole anesthetic agent, they caused a proportional dose-response decrease in regional blood flow to CPP. However, they did not result in intercoronary or transmural redistribution of coronary blood flow in a swine model of chronic coronary artery occlusion.

Reference:

1. Becker LC: Is isoflurane dangerous for patient with coronary artery disease? Anesthesiology 66:259-261, 1987

TITLE: HYPOTENSION FOLLOWING EPIDURAL BLOCKADE IN HIGH RISK PATIENTS IS AVOIDABLE

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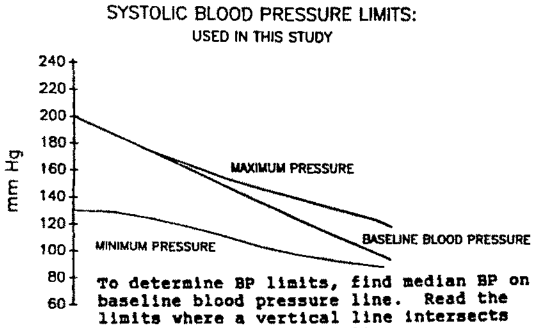
INTRODUCTION: Saada et al have recently shown worsening of segmental wall motion abnormalities after initiation of epidural anesthesia in patients with coronary artery disease undergoing peripheral vascular surgery (1). In their study a standard dose of 12.5 cc of lidocaine 2% was given as a bolus to all patients, and the administration of the anesthetic was associated with blood pressure (BP) decreases potentially causative of the echocardiographic results. We assessed the effects on BP of using a smaller initial volume (8cc) of a slower onset drug, followed by supplemental doses adjusted to achieve an adequate block in patients undergoing lower extremity vascular surgery.

METHODS: With the approval of the Clinical Investigation Committee, nine patients scheduled for lower extremity vascular surgery were studied after written informed consent was obtained. Individualized limits for systolic BPs were defined using the median of three preoperative BPs and the nomogram in figure 1. All patients were monitored with intraarterial catheters, and vital signs were recorded on paper strip charts intraoperatively for later analysis. Patients received 10 cc/Kg crystalloid prior to induction of epidural anesthesia. Following standard sterile prep and drape, #17 ga. Touhy needles were positioned in the epidural space at L2-3 or L3-4, and 3cc bupivicaine 0.75% with epinephrine 1:200,000 was administered through the needle as a test dose. This was followed by 5cc bupivicaine 0.75% plain. An epidural catheter was then placed and secured for subsequent dosing. The level of anesthesia was checked 15 minutes after the initial dose, and if it was less than T8 an additional dose was given. This was repeated every 15 minutes until the level of anesthesia reached T8. The average total dose was 12.6cc (range 8-20cc).

Figure 1



To determine BP limits, find median BP on baseline blood pressure line. Read the limits where a vertical line intersects the maximum and minimum lines.

Paper strip charts were analyzed for time outside patients' individualized upper and lower BP limits. Total minutes out of limits was divided by minutes under observation. Results are reported as mean ± SD. Significance of differences between time points was determined using paired T tests.

RESULTS: Average level of epidural block achieved was T6 (range T2 - T10). The average upper limit for BP was 159 ± 8; the lower limit was 109 ± 8 mm Hg. Minutes outside these limits are shown in figure 2 below. Hypotension was very rare at all time points. Hypertension was more common during the first hour following epidural catheter dosing than subsequently ($p < .005$).

DISCUSSION: Using a volume load prior to induction of anesthesia and a low initial dose of anesthetic followed by incremental doses as needed to obtain satisfactory anesthesia, we were able to achieve adequate anesthesia for lower extremity vascular surgery with virtually no hypotension. Systolic BPs remained at or above their predetermined upper limits more often during the first hour after induction than subsequently. If decreased BP following induction of epidural anesthesia underlies ischemic wall motion abnormalities in high risk patients, then our method of administering the anesthetic was probably protective.

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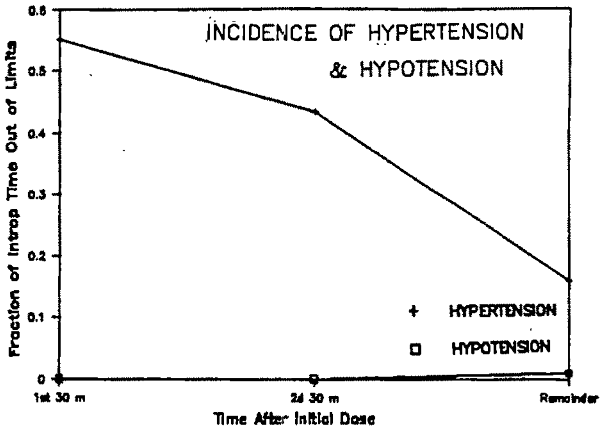
Figure 2



Title: RELATIVE EPIDURAL ANALGESIC POTENCIES OF OPIATES IN TREATMENT OF POSTOPERATIVE PAIN

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Introduction. Postoperative epidural pain treatment is becoming increasingly popular. General recommendations concerning the opiate dosage are lacking. We therefore evaluated the relative analgesic potencies (RAF) of various opiates in treatment of pain after abdominal surgery.

Methods. In 270 patients (age range 25 - 83 yrs) following abdominal surgery in combined general and regional anesthesia, epidural opiates (morphine - mo, n = 107; buprenorphine - bup, n = 17; fentanyl - fen, n = 20; alfentanil - alf, n = 20; tramadol - tra, n = 21; methadone - meth, n = 85) titrated to the patient's individual need for analgesics (1). Opiate consumption (mg) up to 8 p.m. on the 2nd postoperative day was recorded as well as cardiovascular, respiratory or other side-effects. The opiate RAFs were calculated by the ratio morphine : other opiates' consumption.

Results. The opiate RAFs are shown in Table 1, the side-effects under the epidural opiate treatments in Table 2.

Table 1 (AP Mo = 1)

	Bup	Fen	Alf	Tra	Meth
RAF	8	10	1	0.03	0.5

Table 2
Percent of patients suffering from side-effects

	Mo	Bu	Fen	Alf	Tra	Meth
Pruritus	0	0	15	10	0	< 1
Nausea/ Emesis	4	12	15	15	10	15
Urinary retention	17	0	10	0	0	15
Low degree of sedation	0	0	45	35	0	50
Diazepam requirement	28	12	0	0	0	0
Hypotension	0	0	0	0	0	0
Respiratory depression	0	0	0	0	0	0
Pain from bolus	0	0	5	10	14	0

Discussion. The results show that the opiate RAFs differ significantly due to the varying opiate lipophilicities and due to the morphine-different opiate receptor affinities, opiate receptor specificities and opiate receptor bindings characteristics. None of the patients complained of adverse effects would warrant discontinuing the postoperative opiate titration treatments. The method is especially indicated when an epidural catheter has already been placed for intraoperative use. However, some of the observed side-effects, e.g. nausea/emesis and urinary retention in up 20 %, might be attributed to the intraoperative administration of local anesthetics.

Reference
1. Chrubasik J, Wiemers K. Continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief by means of a small, externally worn infusion device. Anesthesiology 1985;62:263-67.

Title: HOLTER MONITORING OF DYSRYTHMIAS IN PATIENTS WITH MYOCARDIAL CONTUSION

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Introduction:

Although improvement has been made in the detection and diagnosis of myocardial contusion (MC)[1,2], much confusion remains on the clinical effects of the injury. While some studies have demonstrated frequent and occasionally lethal dysrythmias[2,3] and abnormalities of cardiac contractility[1,3], others have found minimal cardiac dysfunction in patients who have sustained MC[4]. No large scale prospective study exists which clearly deliniates the hemodynamic and cardiac conduction problems encountered in these patients. In most series, monitoring of dysrythmias has been dependent upon intermittent human observation. In order to examine dysrythmic activity occurring following MC, results of continuous Holter monitoring were correlated with cardiac isoenzymes, clinical findings, and ECG abnormalities.

Methods:

After obtaining Institutional Review Board approval and informed consent, fifty consecutive patients who were admitted to the Presley Trauma Center with definite evidence of blunt chest trauma were enrolled in the study. Patients with a history of previous myocardial infarction, cardiac surgery, cardiac arrest upon admission, positive urine cocaine or amphetamine levels, or were greater than 60 years of age were excluded from the study. Creatinine phosphokinase muscle brain fractions (CPK-MB) were drawn upon admission and every 8 hours for 24 hours. ECG and cardiac output determination (using a Lawrence 9000 Doppler monitor) were obtained at admission and every morning for 3 days. A Holter monitor was placed at admission and recorded for 48 hours in all patients. If CPK-MB was greater than 5%, the patient was considered positive for MC and Holter monitoring and daily ECG were continued for a total of 7 days. The number of patients with dysrythmic events and those with a cardiac index of less than $2L/m^2$ were compared between CPK-MB positive and negative groups using Chi-square analysis.

Results:

Fifteen of the 50 patients sustained a myocardial contusion (mean CPK-MB 14%, range 5.4-30.7). Sinus tachycardia and non-specific ST-T changes occurred with equal incidence in both groups, however RBBB occurred more frequently in MC patients (5/15 vs 3/35, $p < 0.001$). Holter monitoring demonstrated significant dysrhythmic events in 10 of the 15 MC patients and in only 3 of 35 patients with CPK-MB < 5% ($p<0.001$). Dysrythmic events were most frequent on hospital days 1 and 2, but occurred as late as day 6. The majority of dysrhythmic events in the MC group were ventricular tachycardia (7 pts). None of these events were clinically observed despite continuous telemetric monitoring. Mean cardiac index (CI) was not significantly different between the two groups, but 5 of 15 MC patients had CI of < $2.0\ L/m^2$ as compared to 5 of 35 MC negative patients ($p < 0.01$). There was no incidence of cardiac failure and no deaths attributed to the cardiovascular system among these 50 patients.

Discussion:

When continuous Holter monitoring is performed, CPK-MB levels > 5% correlate with the incidence of serious dysrythmias. Routine ECG and telemetric monitoring was inadequate for the detection of these dysrythmias which occur as late as 6 days post injury.

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TITLE: DOES FIBEROPTIC EVALUATION OF ENDOBRONCHIAL TUBE POSITION IMPROVE OUTCOME?

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Introduction. A previous report recommended the use of fiberoptic bronchoscopy (FB) for the correct positioning of double-lumen tubes (DLT) since the incidence of malposition missed by clinical assessment was found to be 48%.[1] However, no attempt was made previously to correlate accuracy of placements with arterial oxygenation (PaO_2) during one-lung ventilation (OLV). The purpose of this study was to assess whether during OLV the properly positioned DLT will necessarily result in better gas exchange when compared with the malpositioned ones.

Methods. After written informed consent had been obtained, 22 adult patients (pts) scheduled for thoracic surgery were studied. Following induction of anesthesia, all pts were intubated with a properly sized, left-sided DLT. The anesthesiologist assigned to the cases determined the correct placement of the tube and satisfactory lung separation by auscultation. A single investigator performed all FB in the supine and then in the lateral position to assess the adequate placement of the DLT. This included bronchoscopy, first via the tracheal lumen to assess patency of the right main bronchus (RMB) and to check that only the upper edge of the bronchial cuff was visualized at the level of the carina. That determined if the DLT was advanced too far in the left main bronchus (T) or not far enough (N) with most of the bronchial cuff bulging over to obstruct the RMB lumen. Then bronchoscopy via the bronchial lumen was performed to visualize and confirm patency of the left upper bronchus. The anesthesiologists responsible for the clinical evaluation and the management of OLV were "blinded" to the bronchoscopic findings.

Results. We studied 10 pts undergoing left thoracotomies (LT) and 12 pts undergoing right thoracotomies (RT) with similar demographic data. Lung separation during OLV was satisfactory in all pts. Table 1 reports the PaO_2 values using 100% oxygen during two-lung ventilation (2LV), during steady state OLV, and the results of the fiberoptic confirmation scored by the endoscopist as N, T, or correct positioning (C). In analyzing the results, we divided the pts into 2 groups according to accuracy of placement. Group I includes 5 pts, 3 RT and 2 LT, in which FB revealed malpositioning. In this group mean PaO_2 during 2 LV was 448±100 mmHg (±SD), while ranging between 183 and 307 mmHg during OLV with a mean of 260±45 mmHg. Group II consisted of pts with correctly positioned DLT. This group was then subdivided based upon oxygenation during OLV into IIA and IIB. The PaO_2 in Group IIA during OLV ranged from 149 to 302 mmHg (mean of 220±63). Group IIB contained 7 pts, 4 RT and 3 LT with a relatively low PaO_2 during OLV, ranging between 53 and 98 mmHg. In this group, mean PaO_2 was 477±96 mmHg during 2 LV and 81±13 mmHg during OLV.

Discussion. As expected, in the 10 pts of Group IIA correct DLT positioning was followed by optimal PaO_2 during OLV (PaO_2 above 148 mmHg). However, in 5 pts (Group I), despite the documented malpositioning by FB, PaO_2 during OLV ranged between 183 and 307 mmHg. The 2 pts in the LT can be easily explained since the DLT being too far in (T) did not influence outcome while the left lung was collapsed. In the 3 RT pts the documented malposition missed by clinical assessment did not prevent achievement of optimal PaO_2 during OLV. On the other hand, in Group IIB, documented correct positioning during OLV resulted in relatively low PaO_2 values. In the patient in which PaO_2 decreased from 463 to 53 mmHg it is possible that the DLT was dislocated as a result of surgical manipulation causing the bronchial cuff to partially obstruct the RMB lumen. From this preliminary data, it appears that the proper positioning of DLT did not necessarily correlate with better arterial oxygenation during OLV, while malpositioning resulted in optimal PaO_2.

The need for FB is well-established, not for the detection of gross malpositioning, but mainly for the fine ones easily missed by clinical assessment, particularly important when absolute lung separation is indicated. However, the recommendations for the routine use of FB in all OLV cases still needs to be further investigated. Our preliminary results do not support this recommendation. A larger number of DLT malpositionings should be correlated with outcome and thus define the need for FB.

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Table 1
PaO_2 Values (mmHg)

	Right Thoracotomies			Left Thoracotomies		
Group	2LV	OLV	Fiberoptic Confirm.	2LV	OLV	Fiberoptic Confirm.
I	507	307	N	516	293	T
	258	183	N	435	236	T
	524	283	T			
IIA	501	301	C	424	187	C
	546	255	C	520	382	C
	527	235	C	354	232	C
	238	187	C	570	150	C
	472	160	C	416	149	C
IIB	413	82	C	257	96	C
	533	84	C	569	98	C
	457	80	C	463	53	C
	368	79	C			

TITLE: SHOULD YOU CANCEL THE OPERATION FOR A CHILDHOOD URI?
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Introduction Although it is desirable to postpone surgery when a child has a "cold", this is often not feasible if the child is from a remote area or the surgery is emergent. We used a large pediatric database (N=29220) to determine if there was an increased perioperative morbidity for children with an Upper Respiratory Tract Infection (URI) undergoing a surgical procedure.

Methods From 1982-87, for each child undergoing surgery, the anesthesiologist completed a form including personal information about the child, existing medical conditions, the site of the procedure, the physical status score (PS), and any intraoperative and recovery complications. Children were divided into five age groups for the purposes of analysis: <1 month, 1-12 months, 1-5 years, 6-10 years and 11+ years. Subsequent to the procedure, for inpatients, a dedicated anesthesia nurse interviewed the child or parents and reviewed the hospital chart recording any complications which may have occurred early in the postoperative period. We compared the rate of perioperative events for children who were identified preoperatively as having an URI with children who did not have an URI.

Results There were 1283 children who had an URI and no other medical conditions and 20876 children without an URI who had no other medical conditions. 57.9% of the URI group were classified as PS 1 as compared to 96.6% of the non-URI group. Children with URI were more likely to be undergoing an ophthalmological or otolaryngological procedure than children without an URI. Children with URI were more likely to be under 5 years of age than the non-URI children. The most frequent age group with an URI was children 1-5 years, 63.45%, while the incidence in children <1 month and 1-12 months was 1.4% and 8.42% respectively.

The rate of intraoperative complications was higher for the children with URI as compared to the non-URI group and this was accounted for by events related to the respiratory system. The rate of airway obstruction was 3.43% for the URI group and 0.76% for the non-URI group. The rate of "other respiratory" problems (breathholding, coughing, laryngospasm and bronchospasm) was 2.73% for the URI group and 0.75% for the non-URI group. A similar result was seen for the recovery room time period where the rate of airway obstruction was 6.94% for the URI group and 3.01% for the non-URI group.

The increased risk for respiratory complications was also seen in the postoperative period. The rate of croup was 3.77% for the URI group as compared to 0.67% for the non-URI group and the rate of other respiratory complications was 6.12% for the URI group as compared to 0.84% for the non-URI children. Furthermore, children with URI were twice as likely to have a problem with temperature regulation in the postoperative period than children without an URI.

The rate of other complications (cardiovascular, surgical or other) were not different between the two groups for the three time periods (intraoperative, recovery room or postoperative).

Discussion In a retrospective study, Tait et al concluded that there was no increase in intraoperative complications associated with patients presenting with uncomplicated URI's. However, in our series, children with an URI were two to three times more likely to have respiratory related problems intraoperatively. In addition, the risk of respiratory complications clearly extended into both the recovery room and early postoperative periods, when children were less likely to be observed by a physician. Our study supports the work of Desoto et al who also reported an increased respiratory morbidity in the postoperative period. We conclude that the administration of general anesthesia to children with an URI is not benign and these children require more observation/management in the postoperative phase of their surgical procedure.

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TITLE: ADMINISTRATION OF ALLOPURINOL PRIOR TO OCCLUSION OF HEPATIC BLOOD FLOW IN THE RAT PREVENTS THE APPEARANCE OF CHEMILUMINESCENCE FOLLOWING REPERFUSION

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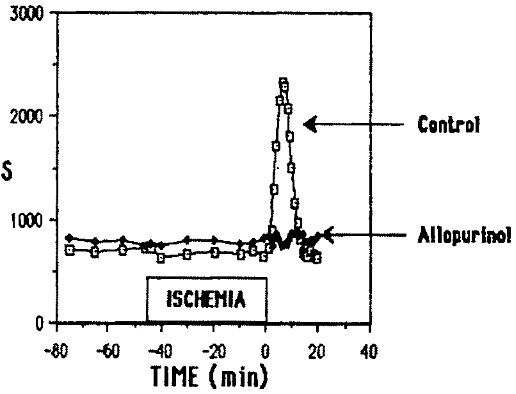
Introduction: The mechanism by which organ damage is produced by prolonged anoxia or ischemia is not understood completely. Although restoration of high energy stores occurs after return of normal oxygen delivery (1), prolonged absence of organ oxygenation produces a chain of events leading to irreversible functional failure. Demopoulos et al (2) hypothesized that products produced by lipoperoxidation following reperfusion may be responsible for this damage. Peroxidative intermediates in the brain are detected in vitro after a hypoxic insult (3). That pathology may be mediated by lipid peroxidation (4) suggests the need for further investigation of this hypothesis. Detection of peroxidative intermediates in vivo after hypoxia or ischemia would be significant, and might suggest an approach to therapy.

It has been suggested that reperfusion following ischemia causes free radical formation (4). In the absence of oxygen, cells cannot maintain ionic gradients and calcium leaks into cytoplasm. Cytoplasmic calcium activates a protease which converts xanthine dehydrogenase to xanthine oxidase. While xanthine dehydrogenase cannot transfer electrons to molecular oxygen, xanthine oxidase can use molecular oxygen when xanthine is oxidized to uric acid. Molecular oxygen supplied during reperfusion leads to formation of superoxide radical and hydrogen peroxide. Lipoperoxidation produced by these highly active free radicals is felt to be a significant cause of reperfusion-induced pathology.

During lipid peroxidation, bioluminescence is produced by reaction of free radical intermediates with surrounding tissue (5), a phenomenon which has been demonstrated in vivo by the appearance of hepatic chemiluminescence in the enzyme-induced rat during administration of chloroform (6). Recent studies have documented a brief burst of chemiluminescence during the first few minutes of reperfusion of the rat liver after 45 minutes of ischemia (7). Allopurinol inhibits the activity of xanthine oxidase; thus, it has been postulated (8) that allopurinol administration prior to ischemia might ameliorate its pathology. Since measurement of chemiluminescence in vivo provides a continuous real-time index of free-radical induced lipoperoxidation, the following study was performed.

Methods: After approval by our Institutional Animal Care and Use Committee, hepatic chemiluminescence was evaluated in six Wistar rats weighing 180-200 g as previously described (7). Allopurinol was administered orally (200 mg/kg) 24 hours and 1 hour before hepatic occlusion (8). Following a 30 minute control period, the hepatic artery and portal vein were gently occluded for 45 minutes. At the end of this time, hepatic blood flow was restored. Chemiluminescence was measured continuously during the control period as well as during occlusion and for 20 minutes after reperfusion.

Results: Light emission (counts per second) remained constant during the control and ischemic measurements. In contrast to data obtained in rats with normal xanthine oxidase activity (7), hepatic light emission did not increase during twenty minutes of observation following reperfusion (figure).



Discussion: Itoh et al (8) demonstrated significant diminution of neurological deficit after reperfusion of the intact rat's brain if allopurinol was administered prior to ischemia. The present study suggests that pathology following ischemia and reperfusion is mediated by free radical formation, an occurrence that may be evaluated by continuous measurement of chemiluminescence. It is concluded that inhibition of xanthine oxidase may prevent free radical formation which follows reperfusion of the ischemic liver.

Supported in part by a University of Pennsylvania Biomedical Research Support Grant.

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Title: BOLUS ESMOLOL AND THE POST-INTUBATION RESPONSE IN PATIENTS INDUCED WITH FENTANYL/THIOPENTAL

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Introduction. Esmolol, a cardioselective, ultra short-acting beta-blocker, has been effective in attenuating the cardiovascular response to intubation when administered as an infusion to lightly anesthetised patients induced with thiopental alone.[1] Few patients with increased risk for the development of myocardial ischemia are anesthetised in this manner. This study was designed to evaluate the effectiveness of the more easily administered bolus esmolol combined with moderate dose fentanyl (5ug/kg) and thiopental (3-5mg/kg) in attenuating the cardiovascular response to intubation in patients with cardiovascular compromise.

Methods. After University Ethics Committee approval and informed consent had been obtained, 45 patients scheduled for noncardiac surgery were entered into a randomized, double-blind, placebo-controlled study. All patients had a history of chronic angina and/or hypertension, were ASA Class II or III, without severe congestive heart failure, conduction delay, or bronchospastic disease. The patients usual medications, including beta-blockers, were continued on the day of surgery. Monitoring equipment consisted of a non-invasive blood pressure monitor set to record blood pressure and pulse at one minute intervals for 15 minutes after drug administration and a Holter monitor to detect arrythmias and ischemic episodes (lead II and V_5). Anesthetic induction was identical in all patients. Fentanyl (5ug/kg) was given 3 minutes prior to induction with thiopental (3-5mg.kg). Patients were randomly allocated to receive either Placebo (PLCB), esmolol 100mg (E100) or esmolol 200mg (E200) ninety seconds prior to intubation. Post-intubation increases in heart rate of blood pressure were treated by increasin the level of anesthesia. Analysis of variance was used to compare the 3 study groups at each study time with the use of baseline HR and SBP as the covariant.

Results. There were 15 patients in each group. One-third of the patients were on chronic beta-blocker therapy and one-fifth on calcium antagonists. The mean age was 65 ± 10 years; mean ward SBP was 153 ± 25, and mean ward HR was 79 ± 10. Hypotension (SBP decrease by 25%) occurred in one patient in the placebo group, one patient in the E100 group, and in three patients in the E200 group. Bradycardia (HR less than 50) was reported in four patients in the placebo group, one patient in the E100 group, and in one patient in the E200 group. No new episodes of ischemia were detected during the fifteen-minute follow-up period. Mean heart rate did not change by a clinically significant amount by any of the three groups. The difference between placebo and each of the esmolol groups did not achieve conventional levels of statistical significance at any point in time (0.5 minutes after intubation p=.055). Compared to baseline, mean systolic blood pressures were lower following induction and intubation in all three groups. Compared to placebo, the mean SBP in each of the esmolol groups was significantly lower 90 seconds after intubation. Post-intubation hypertension occurred in one patient in each group.

HR

	PLCB	E100	E200
Baseline	71	72	73
Post-fentanyl	70	70	74
Post-induction	69	65	67
Post-intubation max.	76	71	73
0.5 min. post-intub.	73	66	67
1.5 min. post-intub.	71	66	67
2.5 min. post-intub.	70	67	67

SBP

	PLCB	E100	E200
Baseline	164	161	151
Post-fentanyl	157	151	155
Post-induction max.	159	141	141
0.5 min. post-intub.	133	121	119
1.5 min. post-intub.	138	116*	116*
2.5 min. post-intub.	134	122	119

*P ≤ .01 (compared to placebo)

Discussion. Bolus esmolol has been shown to blunt the intubation response in patients anesthetised with thiopental (5mg/kg)[2]. Patients at higher risk for myocardial ischemia, those with angina and/or hypertension usually are maintained on chronic medication and receive a balanced anesthetic technique including narcotic. This study has shown that in patients with chronic hypertension and/or angina, and in the presence of 5ug/kg induction dose of fentanyl, esmolol in doses of 100 or 200mg 90 seconds prior to intubation, does not effect the heart rate of blood pressure response to intubation to a degree that is clinically significant. While beneficial clinical effects were not detected, esmolol in the dose of 100 or 200mg can be safely added to an induction dose of 5ug/kg of fentanyl. Bradycardia and hypotension does not occur more frequently following esmolol and fentanyl than following fentanyl alone.

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TITLE: HEMODILUTION AND HYPERTENSION INCREASE CEREBRAL HEMORRHAGE FOLLOWING FOCAL CEREBRAL ISCHEMIA IN RATS

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Introduction: Hypervolemic-hemodilution and hypertension have demonstrated an ability to decrease the extent of focal cerebral ischemia.[1,2] However, such therapy may convey a risk of intracerebral hemorrhage.[3] We evaluated the effect of hypervolemic-hemodilution and hypertension on cerebral hemorrhage following temporary middle cerebral artery occlusion (MCAO) in isoflurane (1.2 MAC) anesthetized Spontaneously Hypertensive rats (n = 28).

Methods: The study protocol was approved by the Animal Research Committee of Loma Linda University. Following orotracheal intubation, the femoral vessels were cannulated and the left middle cerebral artery exposed via a temporal craniectomy. Physiologic parameters (pH, $PaCO_2$, PaO_2, mean arterial pressure [MAP], hematocrit [Hct], weight, and temperature) were monitored. Immediately prior to MCAO one of the following treatments was begun and continued throughout the occlusion period: 1) **Control**-neither Hct, MAP, nor blood volume were manipulated; 2) **Hypervolemic-Hemodilution**-5% albumin was administered to maintain a Hct of 29-32%; 3) **Hypertension**-the MAP was increased by 30 mmHg with a phenylephrine infusion; or 4) **Hypervolemic-Hemodilution/Hypertension**-hypervolemic-hemodilution and phenylephrine induced hypertension were concurrently employed during MCAO. After achieving the desired physiologic state, the middle cerebral artery was occluded with a 10-0 monofilament suture in two locations (proximal and distal to the lenticulostriate branches). The occlusion was maintained for 180 minutes, following which the sutures were released and a 120 minute period of reperfusion was allowed. The brains were harvested and analyzed for tissue concentration of hemoglogin (Hgb) by spectrophotometric assay. Statistical analysis was performed on the physiologic and brain Hgb data by an analysis of variance, and when appropriate a Bonferroni correction factor was applied. A P value <0.05 was considered significant.

Results: There were no significant differences in pH, $PaCO_2$, PaO_2, temperature and weight. There were differences in MAP and Hct (see Table 1). The brain hemoglobin values are listed in Table 2. There was a significant ($P<0.05$) increase in brain hemoglobin content in the hypervolemic-hemodilution and hypertension only groups compared to the Control group. There was an additional increase in brain hemoglobin content in the hypervolemic-hemodilution/hypertension group compared to the other three groups ($P<0.05$).

Discussion: The results of this study indicate that the employment of hypervolemic-hemodilution or hypertension during middle cerebral artery occlusion may effect an increase in cerebral hemorrhage in the rat. When hypervolemic-hemodilution and hypertension were combined, an even greater increase in cerebral hemorrhage was observed. These results indicate that although hypervolemic-hemodilution and hypertension increase cerebral blood flow to ischemic areas of the brain,[1,2] there is a potentially detrimental side effect of such therapy resulting in an increase in cerebral hemorrhage. Further studies are necessary to delineate the appropriate timing of hypervolemic-hemodilution and/or hypertension in order to maximize beneficial effects (↑ CBF) while minimizing potential hazards (↑ hemorrhage).

	Control	H-H	↑ MAP	H-H/↑ MAP
MAP (mmHg)	131 ± 2	129 ± 3	160 ± 1*	160 ± 1*
Hct (%)	47 ± 1	31 ± 1*	48 ± 1	31 ± 1*

Table 1-physiologic values (mean ± SD). H-H is the hypervolemic-hemodilution group. ↑ MAP is the hypertensive group. H-H/↑ MAP is the hypervolemic-hemodilution/hypertensive group.
*$P<0.05$ versus Control.

	Control	H-H	↑ MAP	H-H/↑ MAP
Hgb	2.8 ± 1.9	16.4 ± 12.8*	13.1 ± 10.1*	50.8 ± 30.8*,#

Table 2-brain hemoglobin values (µg of hemoglobin per gram of brain tissue in the hemisphere ipsilateral to MCAO[mean ± SD]).
*$P<0.05$ versus the Control group.
#$P<0.05$ versus the Control, H-H, and ↑ MAP groups. See Figure 1 legend for group abbreviations.

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TITLE: ISOFLURANE MAC IN SPONTANEOUSLY HYPERTENSIVE RATS

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Introduction: While significant interspecies variations in MAC are well known, substantial intraspecies variations in MAC have not been reported.[1] We determined MAC in age matched Sprague-Dawley (n = 8) and Spontaneously Hypertensive rats (SHR [n = 8]).

Methods: The study protocol was approved by the Animal Research Committee of Loma Linda University. Following induction and orotracheal intubation, each rat received isoflurane for a 120 minute anesthetic equilibrium period (1.65% end-tidal [Puritan-Bennett Datex Capnomac infrared anesthetic gas analyzer]). During the first 20 minutes of the equilibrium period a femoral arterial line was placed with attention to avoiding contact with the femoral nerve. The animal was left undisturbed during the remaining 100 minutes of the equilibrium period. Equilibrium was defined as four successive samples of end-tidal isoflurane that differed by less than 5%. Sampling of end-tidal gases was performed every five minutes. Physiologic parameters (pH, $PaCO_2$, PaO_2, mean arterial pressure [MAP], hematocrit, weight, and temperature) were monitored during MAC determination. Isoflurane equilibration was verified at the conclusion of the 120 minute period and MAC determined by the standard tail clamp method.[2] Following the initial tail clamping the end-tidal isoflurane concentration was changed by 10% of the initial concentration, and equilibrium again verified. When the interval containing MAC had been narrowed to less than 10% of the original isoflurane concentration, the mid-point of this interval was then tested. In this manner MAC was narrowed to an isoflurane interval of <5% (0.08%) of the original concentration. A group MAC was calculated for the Sprague-Dawley and SHR groups by averging MAC for all eight animals in each group. The physiologic and MAC data were compared between groups by a group t-test. A P value of <0.05 was considered significant.

Results: There were no between group differences in age, pH, $PaCO_2$, PaO_2, hematocrit, and temperature. There were differences in weight and MAP (see Table 1). Isoflurane MAC (mean ± SD) was significantly less in SHR rats (1.20 ± 0.05% end-tidal) than in Sprague-Dawley rats (1.57 ± 0.08% end-tidal [$P<0.05$]).

Discussion: The results of this study do not support the common assumption that MAC is constant within a given animal species. Two factors may account for the observed difference in MAC. The first is the possibility that the nociceptive threshold is lowered in the hypertensive state.[3] The second concerns reported differences in central neurotransmitter levels between the SHR rat strain and other strains, and a potential influence this may exert on MAC.[4] Further studies are necessary before conclusions addressing the possibility of such a property in humans can be made.

	Sprague-Dawley	SHR
Weight (g)	463 ± 30	371 ± 10*
MAP (mmHg)	101 ± 10	148 ± 13*
Isoflurane MAC (% end-tidal)	1.57 ± 0.08	1.20 ± 0.05*

Table 1-physiologic and MAC data (mean ± SD).
*$P<0.05$ versus the Sprague-Dawley group.

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TITLE: PATIENT COMFORT: A COMPARISON OF TRAIN-OF-FOUR AND DOUBLE BURST STIMULATION

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INTRODUCTION: The assessment of neuromuscular function in the Post Anesthesia Care Unit (PACU) patient who may be experiencing residual blockade would be facilitated by a simple, non-painful means of neurostimulation which did not require quantification with a mechanical recording device. Train-of-Four (TOF) typically is not sensitive enough when evaluated visually or tactilely.[1] While the response to a tetanus is more discernible, such a stimulus is very uncomfortable and generally is not applied to awake patients. Double burst stimulation (DBS) has recently been introduced to improve tactile demonstration of fade, without the need for a five-second tetanus.[1,2] DBS consists of two high-frequency (50 Hz) bursts of stimuli separated by 750 msec. DBS$_{3,3}$ incorporates three stimuli in each burst, whereas only two stimuli are incorporated in the second group of the DBS$_{3,2}$. We undertook the present study in order to evaluate whether this clinically more sensitive means of assessment would be tolerated as well as TOF in awake patients.

METHODS: After approval by the institutional Human Investigation Committee, 20 unmedicated subjects were evaluated. The ulnar nerve was stimulated via cutaneous electrodes with a Myotest (Biometer, Denmark) nerve stimulator. The negative electrode was placed over the olecranon groove, and the positive electrode was placed on the volar forearm. The Myotest was calibrated and tested to confirm consistent current output with each mode of neuromuscular stimulation at the preset amperages. Each subject then received nine sets of neuromuscular stimuli in a randomized order. Thus, TOF, DBS$_{3,2}$ and DBS$_{3,3}$ stimulations were performed at 20 mA, 30 mA, and 50 mA, with a 10-20 second interval between each stimulation. Patients rated their discomfort utilizing a visual analog scale, anchored with 0 = no discomfort and 10 = worst imaginable discomfort. Data were analyzed by ANOVA and expressed as mean ± SD, with $p<0.05$ considered statistically significant.

RESULTS: Significant differences were noted between DBS$_{3,2}$ and TOF and also between DBS$_{3,3}$ and TOF at 20, 30, and 50 mA. There were, however, no significant differences between the two DBS modes of stimulation at any of the amperages tested. Upon stimulation at 50 mA, the mean VAS scores were 4.94 ± 2.56, 7.37 ± 2.10, and 7.58 ± 1.90 for TOF, DBS$_{3,2}$, and DBS$_{3,3}$ respectively. With lesser currents, both DBS and TOF became less uncomfortable (Figure).

DISCUSSION: Residual effects of neuromuscular blocking drugs are not uncommon in PACU patients,[3] and have been implicated as a possible cause of postoperative ventilatory morbidity.[4] It is thus important to properly assess the adequacy of reversal. The ideal means of assessing neuromuscular blockade in the awake patient remains to be determined. DBS has been reported to be more sensitive in the tactile detection of fade than is TOF.[1,2] However, the present data indicate that DBS is also significantly more uncomfortable. One could argue that if weakness in the PACU were suspected, a redosing of the reversal agents would insure adequate return of function. However, overdosage with anticholinesterases can potentiate blockade, rather than reverse it. Thus, in view of the potential morbidity associated with residual neuromuscular blockade, and the severe discomfort associated with tetanus in awake patients, we conclude that DBS is a reasonable choice when weakness is suspected and a mechanogram or other recording device is not readily available.

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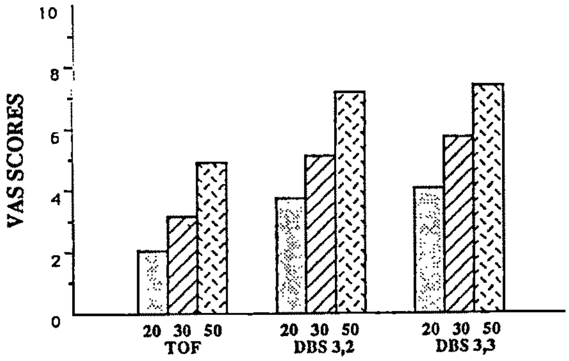

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Title: Impaired Learning and Recall After IV Sedation: Implications for Outpatients

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Introduction. An increasing proportion of surgery is now being performed on an outpatient basis. Even in procedures performed under local, anesthesia most patients receive at least minimum iv sedation. Regional nerve blocks may require even more sedation. Street-fitness is usually a subjective evaluation of level of consciousness by the recovery room personnel and the discharging physician. This randomized, prospective double-blinded study compared the subjective evaluation of cognitive functioning with a specific age-independent measure of acquisition and recall of information. In addition, since a high proportion of our population include present or past alcohol abusors this variable was also considered in the ability to learn and recall information after iv sedation.

Methods. After institutional review board approval and informed consent thirty-eight male patients age 26-90 years were randomly divided into 5 iv sedation groups:

I. Normal Saline
II. Midazolam .01 mg/kg
III. Diazepam .03 mg/kg
IV. Nalbuphine .1 mg/kg
V. Nalbuphine .1 mg/kg and Droperidol .02 mg/kg

Patients underwent inguinal hernia repair or transurethral prostatic resection under spinal anesthesia (SAB). They received no preoperative medication except the continuation of antihypertensives and were not taking pain or psychotropic medications. The patients' cognitive functioning was evaluated pre operatively in their rooms the night before surgery and post operatively in the post anesthesia recovery room (RR). Anesthetists blinded to the patient's sedation group, rated their level of awareness upon arrival in the operating room, after SAB, and in the RR prior to discharge.

Specifically the psychological testing, the Randt memory test with two equivalent forms, included 8 subtests evaluating: orientation, short term acquisition and recall, auditory recall of non-meaningful and logical material, acquisition and recall of new associations, and incidental recall. A total memory quotient was also computed. All scores were standardized to same age controls. Therefore, the score of elderly patients was standardized to other patients their age and the drug effect would not be obscured by age-related cognitive effects.(1)

Data were analyzed using multifactoral ANOVA, regression analysis and t test, as appropriate, looking for sedation, age or alcohol effect on cognitive performance as compared to baseline.

Results. Prior to iv sedation the five groups were equivalent in age, pre test performance (individual tests and total score) and presence of ETOH abuse. Patients receiving diazepam, nalbuphine and nalbuphine/droperidol showed no impairment from their baseline performance. However, patients receiving only normal saline had a marked decrease in verbatim recall ($p < .01$) and total score ($p < .002$). The greatest impairments was found post operatively in patients receiving midazolam. These patients had difficulty in 4 subtests evaluating short term acquisition ($p < .05$) and recall, ($p < .01$) new associations acquisitions ($p < .04$) and recall ($p < .03$) and total score ($p < .01$). Interestingly, there was no correlation between observer evaluation of alertness of patients and their test performance. Finally, patients with a history of alcohol abuse showed less impairment than their sober cohorts in total score ($p < .006$) and on specific subtests.

Discussion. This study warns that subjective evaluation of alertness may not reflect cognitive functioning after surgical procedures. Unlike diazepam, nalbuphine and droperidol, minimal doses of midazolam does cause a significant decrement in acquiring and recalling new information (e.g. post operative directions). This impairment was not detectable by patient interview. Although patients receiving no sedation were able to acquire and recall information, they were unable to recall logical groups of words after the stimulation and stress of an operation. Interestingly, the patients who had a history of post or present alcohol abuse maintained this ability to acquire and recall paired information better than their sober cohorts. Finally, in an objective test with performance standardized for age, there were no specific age related differences in cognitive functioning in any of the treatment groups.

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TITLE: EFFICACY OF BICITRA AS A PREOPERATIVE ANTACID FOR AMBULATORY SURGICAL PATIENTS

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INTRODUCTION: Ambulatory surgical patients have been shown to have gastric volumes which are larger and more acid than in-patients.(1) They may therefore be at greater risk of aspiration pneumonitis should regurgitation occur. The purpose of this study was to assess the efficacy of Bicitra^{R} (Willen Drug Co., Baltimore, Maryland), a commercial preparation of sodium citrate, in modifying intragastric pH and volume in ambulatory surgical patients.

METHODS: Following Institutional Review Board approval, written informed consent was obtained from 80 out-patients presenting for elective orthopedic or plastic surgical procedures. All patients were ASA general health categories 1 or 2 and between the ages of 18 and 65 years. Pregnant patients were excluded, as were those with gross obesity greater than 100 kg, those with gastrointestinal pathology, and those taking drugs known to interfere with intragastric pH or motility. No preoperative medications were prescribed. Patients were fasted for at least eight hours and randomly allocated into one of four groups: Nil by mouth (Group 1), water 30 ml (Group 2), Bicitra 15 ml (Group 3), or Bicitra 30 ml (Group 4), administered in a blind manner at varying times from 5 minutes to 125 minutes preoperatively. A standard general anesthetic technique was used and time from administration of antacid or control until anesthetic induction noted. Following induction, an 18 gauge Salem-sump gastric tube was passed and a 5 ml sample taken for pH measurement using a Beckman 3500 pH electrode.

Intragastric volume was then measured using the polyethylene glycol (PEG) dilution technique (2); 250 ml of 0.3% PEG was instilled via the gastric tube and barbotaged for 30 seconds to ensure complete mixing. A sample was removed and the final PEG concentration measured by Perkin-Elmer spectrophotometer. The initial intragastric volume could then be calculated from the change in PEG concentration.

Volume and pH results were compared using the Mann Whitney U-test, the number of patients with $pH > 2.5$ in each group were then compared using the Fisher Exact test. A p value < 0.05 was considered statistically significant.

RESULTS: No differences in patient demographic data, smoking habits, or time from antacid administration until anesthesia and gastric sampling (range 5 to 125 minutes) occurred among groups. Mean ± SD pH values for the four groups were Group 1 pH 1.70 ± 0.82, Group 2 pH 2.44 ± 2.25, Group 3 pH 2.76 ± 1.22, and Group 4 pH 4.14 ± 0.53.

The pH in Group 4 was significantly higher compared to other groups ($p < 0.0015$). There were no significant pH differences between the other groups. All patients in Group 4 sampled before 85 minutes had a pH greater than 2.5 (range 3.2 to 5.3); this was significantly more than Group 3 (Bicitra 15 mls) or control ($p < 0.005$). Intragastric volume was not significantly different among the groups; Mean 61 ml ± 51 SD (range 16 to 218 ml).

DISCUSSION: The need for antacid prophylaxis in obstetric patients prior to anesthesia is now accepted. This practice could also be extended to other at-risk groups, including ambulatory surgery patients, in order to protect against acid aspiration syndrome (AAS). H_2-blocking agents administered at least one hour preoperatively usefully decrease gastric acid secretion but may not effectively neutralize acid already in the stomach.(3) These agents are most effective if also given on the evening prior to surgery but this may not always be possible with out-patients whose compliance may be unpredictable.

The oral administration of 15 ml, 0.3 M sodium citrate preoperatively has been shown to effectively increase intragastric pH to greater than 2.5 in routine surgical cases.(4) Bicitra has been shown to be an effective commercial alternative despite its lower pH.

Our results confirmed the presence of high volume and low pH in the gastric contents of ambulatory patients. Bicitra 15 ml did not effectively increase gastric pH above 2.5. Bicitra 30 ml was effective in raising pH above 2.5 in all patients if administered up to 85 minutes prior to anesthetic induction. In view of the large intragastric volumes, the risk of regurgitation is not abolished but the use of 30 mls Bicitra will reduce the risk of AAS should regurgitation and aspiration occur.

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TITLE: **PATIENT CONTROLLED ANALGESIA AFTER CARDIAC SURGERY**

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INTRODUCTION: After cardiac surgery inadequate pain management may play a large role in early morbidity, resulting in cardiovascular lability(1),splinting and ineffective cough(2), and postoperative stress(3). Studies on the use of patient controlled analgesia (PCA) after a variety of other surgical procedures have demonstrated better pain control with less total drug and fewer side effects(4,5); data on the use of intravenous PCA after cardiac surgery are lacking.

METHODS: After obtaining institutional approval and informed consent, 60 patients scheduled for coronary artery bypass grafting were randomized to have post-operative analgesia provided by PCA with i.v. morphine or Conventional Therapy consisting of nurse administered i.v. and i.m. morphine followed by p.o. analgesics when tolerated. PCA was managed using a morphine dose of 0.01 - 0.02 mg/kg with a lockout interval of 15 to 20 minutes; no loading dose or continuous infusion were used. A total of 8 patients were dropped from the study for the following reasons: 1 intraoperative death, 3 with postoperative neurologic deficits precluding study, 2 when PCA was stopped due to lack of understanding by the bedside care team and 2 dropped due to inadequate data collection. This yielded 27 patients in the PCA group and 25 patients in the conventional group. The two groups were similiar with regards to age, gender, percent reoperations, pre-op LV function, pre-existing medical problems, and intra operative course. Anesthesia consisted of high dose fentanyl(77.1 ug/kg) or sufentanil(13 ug/kg) with enflurane, and the same surgeon performed all the operations. Time of entry into the study was taken as the time of extubation and the study continued for 72 hours post-op. Patients underwent bedside spirometry pre-op and if randomized to PCA they were instructed in the use of the pump; all patients were instructed in use of the Visual Analog Scale (VAS) to assess pain with 0 = no pain and 10 = the worst possible pain. For 16 patients in each group pain was assessed with VAS both at rest and on using the incentive spirometer. Data was collected at time of extubation and every 8 hours thereafter until 72 hours post extubation (4th post-op day); data included VAS, Sedation Score (5 point scale, assessed by nurse), vital capacity, peak expiratory flows, respiratory rate, O2 saturation, heart rate, and mean arterial pressure. The following clinical events were prospectively evaluated and recorded: dysrhythmias, hypotension/hypertension, institution of any vasoactive drugs(dilators, pressors, inotropes), fluid requirements, myocardial ischemia/ infarction, need for reintubation, respiratory care needs (naso-tracheal suction, CPAP mask), administration of sedative/hypnotics, delerium or agitation and time of discharge from the ICU. Data were analyzed using PC SAS with univariate analysis by Chi square, single tailed t-test, or Fisher's Exact test as appropriate; p<0.05 was considered significant.

RESULTS: Although control of post-op pain judged by mean daily VAS was virtually identical between groups both at rest and with incentive spirometry(figure 1; all p values > 0.05), the incidence of severe pain (any average daily VAS at rest greater than or equal to 5) was significantly higher in the Conventional Therapy Group (6 of 25) than the PCA Group(0 of 27) (table 2). Vital capacity was somewhat larger on the second and third day of study in the PCA Group (table 1) but this did not achieve statistical significance (p =0.14). Three patients in each group had significant hypoxemia (sat < 90%, requiring high flow oxygen) though no patients were reintubated or managed with mask CPAP. There were no differences between groups in sedation scores, hemodynamic parameters, or incidence of post op complications. Two patients in the Conventional Therapy Group had transient hypotension with parenteral morphine which responded to elevation of the legs. Overall pain scores were low just after extubation, higher on second and third post op day and lowest on the fourth post-op day (figure 1), although day to day comparisions did not achieve statistical significance.

DISCUSSION: The intensity and pattern of pain after cardiac surgery in this study is similiar to that previcusly reported(1,4). PCA appears to be effective in decreasing the incidence of severe pain on the second and third post-operative day and may be responsible for a small increment in vital capacity on the third and fourth post-op day. There were no differences in the any hemodynamic parameters evaluated and no difference in complication rates with the exception of the two episodes of hypotension noted. On the third day of study most patients in the conventional group were receiving oral codiene or propoxyphene and this was as effective as PCA in managing post-op pain. It would appear that PCA is useful in the management of pain after cardiac surgery in the period between extubation and the return of gastrointestinal function and that PCA is at least as safe as conventional therapy and may offer some advantages.

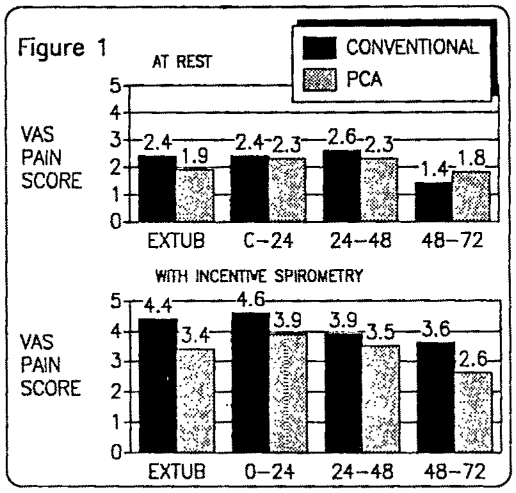
Figure 1

Table 1 FVC (liters)

	CONVENTIONAL		PCA	
	MEAN	S.E.	MEAN	S.E.
PRE–OP	3.04	.16	3.18	.16
EXTUB	1.68	.10	1.75	.12
24 HR	1.35	.08	1.45	.10
48 HR	1.22	.07	1.38	.08
72 HR	1.44	.08	1.62	.09

Table 2 # OF PATIENTS WITH VAS > 5

	CONVENTIONAL	PCA
EXTUB	3	3
0–24 HR	3	0
24–48 HR	4	0
48–72 HR	0	0
TOTAL 0–72	6	0 *

* P = 0.009 (Fisher's Exact)

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TITLE: WARMING DURING CARDIOPULMONARY BYPASS IS ASSOCIATED WITH JUGULAR BULB DESATURATION

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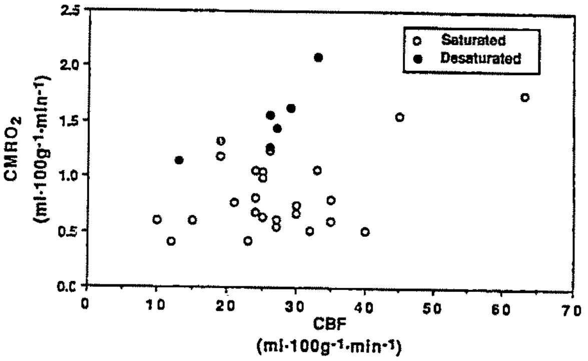
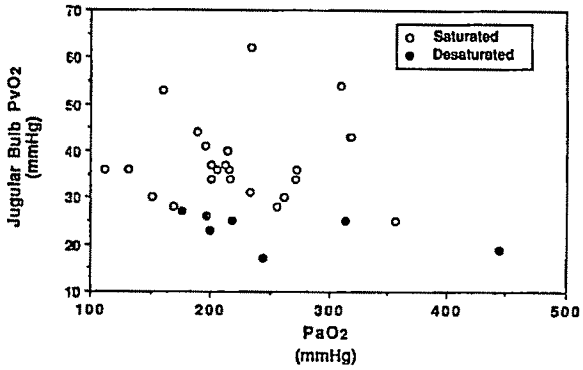
Introduction: One of the most serious complications of cardiopulmonary bypass is postoperative neuropsychologic dysfunction. It has been suggested that this results from intraoperative cerebral hypoperfusion and cerebral ischemia. A possible mechanism of cerebral ischemia could be an imbalance in global oxygen supply:demand, especially during normothermic perfusion where the protection of hypothermia is absent. The primary objective of this study was to precisely characterize cerebral venous oxygenation during rewarming (normothermia) cardiopulmonary bypass in patients managed by alpha-stat control (temperature-uncorrected $PaCO_2$ maintained at 40 mmHg) of arterial blood gases. Jugular bulb PvO_2 was used as a reflection of cerebral oxygen balance.

Methods: Following institutional review board approval and written informed consent, average cerebral blood flow (CBF) and cerebral metabolic oxygen consumption ($CMRO_2$) were measured in 31 patients using Xenon^{133} clearance methodology[1] employing two extracranial gamma emission detectors placed over the right and left parietal lobes during nonpulsatile normothermic cardiopulmonary bypass. The ratio of CBF to $CMRO_2$ was calculated. Patients also participated in an extensive series of neuropsychological and neurological exams preoperatively and 6 days postoperatively. Routine monitoring catheters were placed and a catheter was placed in the right jugular bulb by retrograde internal jugular approach for cerebral venous sampling. Anesthetic management prior to and during cardiopulmonary bypass consisted of diazepam and methadone premedication, then midazolam and fentanyl administered by a pharmacokinetic model-driven drug infusion system which maintained plasma levels of fentanyl at 5 ng/ml and midazolam at 75 ng/ml. Bypass pump flow was kept constant at 2.0 L/min/m^2, PaO_2 >150 mmHg, PCO_2 35-40 mmHg and mean arterial pressure kept between 60 and 80 mmHg. All patients were oxygenated during CPB with a CML Cobe membrane lung oxygenator.

Results: Jugular bulb venous oxygen saturation fell below 70% in 56% of the patients was $\leq$50% in 22% of the patients. Jugular bulb PvO_2 measurements fell below 40 mmHg in 65% of the patients and was $\leq$ 25 mmHg in 23% of the patients. Patients with a PvO2 <25 or SvO2 <50% were considered desaturated (Group D) while the other 24 patients remained saturated (Group S). $CMRO_2$ and CBF are displayed in figure 1. $CMRO_2$ was significantly (P<.005) higher in the group of patients that markedly desaturated. There is no significant difference in CBF between groups: the CBF:$CMRO_2$ ratios were 37±15.3 (Group S) and 16±3.0 (Group D) (P<.03). There is no correlation between PaO_2 and PvO_2.(Figure 2) Review of seven neuropsychological test results indicate a decrease in neuropsychological function from pre to post surgery. Group differences were not significantly different between the 7 patients with desaturation and the 24 others perhaps because of small sample size.

Discussion: These data show that rewarming during CPB is a time when a significant percentage (23%) of patients have PvO2 of less than 25 mmHg. This occurs primarily because of a disproportionate CMRO2 to CBF ratio. The PaO2 does not predict low PvO2 (figure 2) and thus the clinician cannot rely on systemic oxygenation to predict adequate brain oxygenation.





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TITLE: SAFETY OF RAPIDLY ADMINISTERED FLUMAZENIL IN PATIENTS WITH ISCHEMIC HEART DISEASE

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Introduction: Flumazenil is a new benzodiazepine (BZ) antagonist. The clinical pharmacology of this drug has not been fully elucidated, especially the cardiovascular effects of flumazenil alone. F has been shown previously not to effect hemodynamics given slowly when used alone in patients with ischemic heart disease.[1] The purpose of this study was to determine if higher doses of flumazenil produced an effect on hemodynamics when administered rapidly.

Methods: With institutional approval and informed consent 12 patients with class III-IV angina were entered into this double blind randomized placebo controlled study. An ambulatory ECG monitor was placed on the patients approximately 18 hours prior to surgery. BZs were withheld for two weeks prior to surgery. Patients were premedicated with secobarbital 100-200 mg PO and morphine 0.12 mg/kg IM 90 minutes prior to study. Routine invasive monitoring catheters were placed. The ECG was monitored for heart rate (HR), rhythm and ST segment changes in leads I, II and V. Flumazenil (F) or equal volumes of placebo (P) were given in divided doses every 3 minutes (1 mg, 1 mg, 1 mg). Complete hemodynamic profiles were obtained at baseline, 2 minutes after each injection, 5 and 10 minutes after the last injection. To detect alterations in consciousness patients performed a subjective sedation rating at baseline and 10 minutes after the last injection. Data within and between groups were compared using analysis of variance to detect significant ($p<.05$) differences between groups and within groups. Chi square analysis was performed to test differences in nonparametric variables.

Results: The groups had similar demographics. (Table 1) The hemodynamic values are in table 2 and reflect very little change from baseline in either group. There was a slight but statistically significant decrease in blood diastolic pressure after F. The change in mean sedation score was not statistically different (placebo=4.4 mm, flumazenil=8 mm). Postoperative complications are listed in table 3 and were similar in both groups. There was not a statistically significant increase in ventricular irritability during F administration however two patients had nonsustained runs of ventricular tachycardia postoperatively in the F group.

Discussion: Benzodiazepines like midazolam and diazepam have small but significant hemodynamic effects in patients with ischemic heart disease. Flumazenil administration resulted in a slight decrease in blood pressure however unlike benzodiazepine agonists is devoid of other hemodynamic effects.[2] Flumazenil also was devoid of any CNS effect, unlike the benzodiazepine agonist compounds. We conclude that F is safe when administered in relatively high doses to ischemic heart disease patients. This study gives new information regarding the clinical cardiovascular pharmacology of flumazenil. These data are important since it is essential to know the effect of an antagonist alone as well as when given to reverse an agonist.

Table 1. Demographics

	Female	Male	BSA	Age
Flumazenil	1	5	1.92m^2	60 yrs
Placebo	1	5	1.91m^2	61 yrs

Table 2. Hemodynamic Variables

Min		0	2	5	8	11	16
SBP	F	147±13.9	142±20.4	133±20.3	139±19.3	138±23.3	140±24.5
	P	125±13.5	123±12.9	128±11.5	125± 8.8	127±10.6	125±12.1
DBP	F	74±14.8	68±13.9*	68±14.2*	66±12.6*	68±12.7*	68±13.2*
	P	62±09.4	60±09.5	64±10.9	62±12.3	64±11.1	64±11.9
HR	F	60±08.9	58±08.3	55±7.5	59±10.2	58±9.1	59±9.2
	P	60±14.1	60±14.9	59±13.2	61±13.9	61±14.6	60±14.7
PCWP	F	13±02.0	13±01.8	13±1.3	14±1.9	13±1.09	13±2
	P	16±02.1	17±03.5	17±5.3	18±4.9	17±4.9	16±3.3
CI	F	2±00.6	2±00.3	2±0.5	3±0.6	3±0.5	3±0.5
	P	3±00.7	3±00.7	2±0.6*	3±1.04	3±0.6	3±0.6
RAP	F	9±03.8	9±04.4	10±4.1	9±3.8	9±3.5	10±3.2
	P	10±03.1	11±03.1	12±3.4	12±2.9	12±3.4*	12±3.2

*P>0.05 from baseline

Table 3. Postoperative Complications

	Placebo	Flumazenil
Hypotension	2	2
Mild renal insuff.	0	1
Vent. tachycardia	0	2
Anxiety	2	2

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TITLE: MORE BETA BLOCKERS ARE REQUIRED TO CONTROL TACHYCARDIA IN GENERAL THAN EPIDURAL ANESTHESIA.

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INTRODUCTION: Tachycardia (TACH) may increase the probability of myocardial ischemia in patients at risk. The incidence of TACH and efforts to control it in the operating room have not been well studied. Therefore we compared TACH and beta blocker (BB) administration in patients with peripheral vascular disease (PVD) who randomized to epidural anesthesia (EA) or general anesthesia (GA) both intraoperatively (INTRAOP) and postoperatively (POSTOP).

METHODS: Patients who were scheduled for lower extremity vascular grafting and had given written informed consent were studied with institutional approval. TACH was defined as HR > 85 for patients in sinus rhythm and > 100 for patients in atrial fibrillation. Patients were randomized to receive either EA or GA. Both types of anesthesia were administered according to a protocol. GA was induced with fentanyl and thiamylal and maintained with O_2:N_2O and enflurane. Sensory blockade with EA was maintained at T8. Postoperative analgesia was provided with a continuous epidural fentanyl infusion for those patients who randomized to EA, and with a patient controlled intravenous morphine pump for those who randomized to GA. HR was maintained within limits by first adjusting the anesthetic or volume status. BB were then administered if further treatment was necessary. BB administration was standardized as minutes of therapy over total minutes in the operating room or Intensive Care Unit. Bolus doses were assigned a minute value based upon half-life. Variables were analyzed using unpaired T tests. $P < .05$ was accepted as significant.

RESULTS: 32 patients were studied, 17 randomized to EA and 15 to GA. Differences in the incidence of Tach were not significant INTRAOP or POSTOP in either group. The time out of limits INTRAOP was low and similar between the 2 groups, however in order to maintain this relationship more BBs were required in the GA group INTRAOP (fig. 2). Likewise more BBs were required in the GA group POSTOP.

DISCUSSION: It is interesting that the GA group tended to require more BBs INTRAOP to keep the HR within limits, even though the incidence of TACH was similar in both groups. Also, more BBs were required to control TACH POSTOP. In spite of increased BB administration, TACH tended to be more common in GA patients POSTOP. If control of HR is important in relieving rate related ischemia EA may be beneficial.

Figure 1

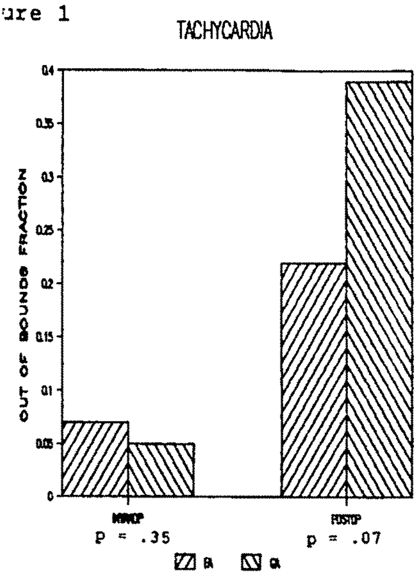
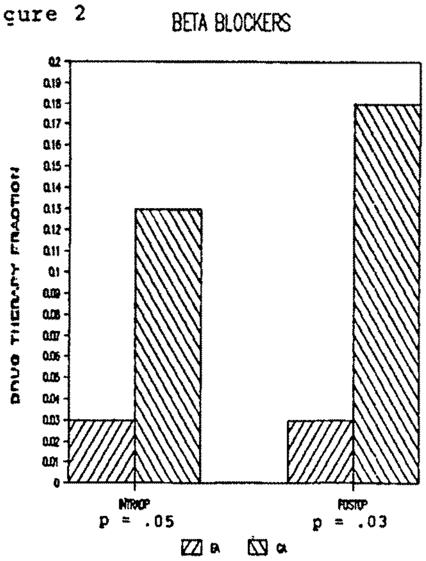


Figure 2



TITLE : ALFENTANIL SUFENTANIL AND FENTANYL:EFFECT ON CEREBRAL PERFUSION PRESSURE

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INTRODUCTION

It is common practice to use one of the short-acting potent narcotics during neurosurgical procedures. Fentanyl, and more recently Sufentanil and Alfentanil, have been used because they provide stable hemodynamics, and allow rapid onset and rapid awakening, particularly in neurovascular procedures. Recently the suitability of Sufentanil and Alfentanil has been questioned regarding their use in patients with increased intra-cranial pressure or compromised intracranial compliance(1). The purpose of this study has been to investigate and compare the effects of Fentanyl, Sufentanil and Alfentanil on cerebrospinal fluid pressure (CSFP) in patients undergoing neurosurgical procedures for intracranial aneurysms or arteriovenous malformations.

METHODS

Approval was obtained from the institutional human investigation committee and written informed consent obtained from each study patient. Each of the 40 patients studied was randomly assigned to one of three groups. Anesthesia was induced in all groups with fentanyl 2 ug/kg, thiopental in titrated dosage, an intubating dose of vecuronium, and lidocaine 1.5 mg/kg. Anesthesia was maintained with isoflurane ≤ 1% in oxygen and air with mechanical ventilation to maintain a constant end tidal CO2 between 30 and 35 mmHg. Arterial catheter and central venous catheter were installed after induction of anesthesia. Then, with the patient in lateral decubitus position a lumbar subarachnoid catheter was installed. CSFP and arterial pressure transducers were zeroed and calibrated at mid-vertebral column level with patients maintained in lateral position, and any further sensory stimulation was avoided. Mean arterial pressure (MAP), heart rate, and CSFP were measured continuously and recorded at 2 minute intervals throughout the 20 minute study period. Control values of these parameters as well as arteriel blood gas tension were obtained after a 10 minute stabilization period, immediately prior to injection of the study drug. With the observer blinded to the study drug identity, group A patients then received 20 ug/kg alfentanil, group S, 0.4 ug/kg sufentanil, and group F, 2 ug/kg fentanyl. Recording of parameters then continued for 10 minutes. Cerebral perfusion pressure (CPP) was calculated as MAP-CSFP. Statistical analyses were performed using Student's t-test and ANOVA as appropriate. Statistical significance was considered as $p < 0.05$.

RESULTS

Twelve patients were studied in group A and 14 patients in each of groups S and F. There were no significant differences among the groups in age, Botterell's grade, incidence of subarachnoid hemorrhage, arterial carbon dioxide tension, (34.4 ± 2.6, 34.1 ± 3.5, 34.8 ± 2.7 mmHg, mean ± S.D. for the A, S and F groups respectively) control mean arterial pressure, or time from induction to administration of the study drug (52 minutes). In all three groups MAP decreased significantly and CSFP rose significantly after administration of the study drug, resulting in a significant decrease in CPP. (Table). However there was no significant difference among the three groups with respect to this effect on CPP and it had diminished by the end of the study period, although only in the alfentanil group was the decrease in CPP no longer significant at that time.

DISCUSSION

Under conditions of our study there appears to be no difference among the 3 narcotics studied as to their effects on CPP, contrary to differences reported by Marx et al. Although the drop in CPP was statistically significant for all 3 drugs, whether or not these changes are clinically significant should be considered while taking into account the end to which the 3 narcotics are used: hemodynamic stability and adequate CPP. We conclude that alfentanil, sufentanil and fentanyl, under conditions of this study, may be equally useful if a mild decrease in CPP would be compatible with the goals of the anesthetic.

Reference:

1.Marx W, Shaw N, Long C, Arbit E, Galicich J, Mascott C, Mallya K, Bedford R. Sufentanil, alfentanil and fentanyl: impact on CSF pressure in patients with brain tumors. Anesthesiology 1988; 69:A627.

TABLE
MEAN ± S.D.
* = SIGNIFICANT P->0.05

	Control CSFP	Peak change CSFP	Control CPP
Drug group			
Alfentanil(A)	6.0±3.8	+1.5±2*	66.8±15
Sufentanil(S)	10.2±6.5	+1.4±1.5*	66.3±11.3
Fentanyl (F)	10.0±4.0	+0.6±0.8*	64.7±9.4

	Peak change CPP	CPP at 10 minutes
Drug group		
Alfentanil(A)	-15.3±7.3*	61.6±10.1
Sufentanil(S)	-12.9±6.8*	56.5±12.2
Fentanyl(F)	-11.4±7.5*	57.0±7

TABLE: Changes in cerebrospinal fluid pressure (CSFP) and cerebral perfusion pressure (CPP) after administration of alfentanil, sufentanil and fentanyl. Values are mean ± S.D. Asterisks indicate significance at p<0.05 level.

Title: MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION DURING HYPOCAPNIA IN HEMODILUTED, ANESTHETIZED DOGS

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Introduction. Hypocapnia impairs myocardial oxygen delivery by the combined effects of reduced coronary blood flow secondary to vasoconstriction and increased hemoglobin-oxygen affinity (1). Although the myocardium can apparently tolerate these effects under conditions of normal hematocrit (2), this may not be the case during hemodilution when myocardial oxygen supply is already jeopardized by reduced oxygen carrying capacity of the blood. Such information has gained increasing clinical relevance recently because of the widening use of cell-free plasma expanders to avoid the risks involved in autologous blood transfusions. The present study was conducted to evaluate changes in myocardial oxygen supply and consumption during hypocapnia in the presence of isovolemic hemodilution.

Methods. The study was conducted in compliance with the requirements of our institution Animal Investigation Committee. Twelve conditioned, large mongrel dogs were studied. The dogs underwent tracheal intubation and left thoracotomy, and were anesthetized with 0.9 % halothane while mechanically ventilated with FIO2 = 1.0. Initially, dead space tubing (volume of 300 ml) was added to the endotracheal tube with tidal volume and ventilatory rate adjusted to maintain arterial PCO2 at a physiological value. Aortic pressure (AOP) and heart rate (HR) were monitored. Radioactive microspheres (15 u) were injected into the left atrium to measure regional myocardial blood flow. Mean transmural myocardial blood flow (MBF) in each heart was computed from the average of blood flow values in the epicardium, midmyocardium, and endocardium. Arterial and coronary sinus blood samples were analyzed for oxygen content (CO-Oximeter) and plasma lactate concentration (enzymatic method). Myocardial oxygen (MVO2) and lactate consumption (MVL) were calculated using the Fick equation. After control measurements were obtained, isovolemic hemodilution (HD) was produced by removing blood from a carotid artery at a rate of 20 ml/min and replacing it intravenously with 5 % dextran-40 at the same rate. The total volume exchanged was equal to 45 ml/kg body weight. After the preparation was allowed to stabilize for 15 min following completion of fluid exchange, measurements during HD alone were obtained. Then while maintaining the hemodiluted condition, hypocapnia (HYPOC) was induced by removal of dead space tubing without change in mechanical ventilation. The hypocapnic condition was maintained for at least 20 min before hemodynamic measurements were obtained. The initial seven dogs studied (Group 1) demonstrated reductions in AOP during HYPOC in the presence of HD. To evaluate the role of this factor, the additional five dogs (Group 2) were studied with a controlled pressure blood reservoir to maintain AOP constant (3). Statistical analyses were performed using ANOVA and Student-Newman-Keuls test and Student's t test.

Results. Control values (mean ± S.E.) for systemic hemodynamic parameters were unremarkable (AOP, 82 ± 5 mmHg; HR, 135 ± 4 b/min; PaO2, 358 ± 39 mmHg; PaCO2, 39 ± 1 mmHg; pHa, 7.38 ± 0.01; Hct, 42 ± 1 %; arterial lactate, 2.9 ± 0.5 meq/l). Systemic responses to HD alone (Hct, 20 ± 1 %) and combined with HYPOC (PCO2, 25 ± 1 mmHg; pHa, 7.55 ± 0.01) were similar for Groups 1 and 2, except that in Group 1 heart rate increased (+ 13%) during HD alone, and AOP decreased (-16%) and arterial lactate concentration increased (+188%) during combined HD-HYPOC. These effects were not evident in Group 2. Myocardial responses during HD alone and combined with HYPOC were not significantly different in Groups 1 and 2. Thus the results were pooled and presented in Table 1. HD alone decreased coronary (A-V) O2 difference, but increases in MBF were sufficient to hold coronary sinus PO2 and MVO2 constant, and to maintain MVL. Although HYPOC during HD reduced coronary sinus PO2, MBF, MVO2, and MVL were not affected.

Discussion. The present findings suggest no imbalance between myocardial oxygen supply and demand during combined hypocapnia and hemodilution whether or not aortic pressure was controlled. This was apparently attributable to 1) the tendency for metabolic vasodilator mechanisms to override the effects of both hypocapnia-induced vasoconstriction and reduced perfusion pressure in control of myocardial blood flow, and 2) the ability of the myocardium to adapt to reduced driving pressure for diffusion of O2, i.e., decreased intracapillary PO2 as reflected in values for coronary sinus PO2. The elevated arterial lactate concentrations in Group 1 imply ischemia in peripheral tissues during combined hemodilution and hypocapnia in the absence of controlled arterial blood pressure.

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Table 1. Myocardial values during HD alone, and during HD-HYPOC.

	CONTROL	HD	HD-HYPOC
MVO2, ml/min/100g	6.2 ± 0.7	6.5 ± 0.6	6.8 ± 0.8
MBF, ml/min/100g	50 ± 4	105 ± 10*	106 ± 13*
A-V O2 diff., vol%	12.4 ± 0.9	6.2 ± 0.3*	6.4 ± 0.3*
Coronary sinus PO2, mmHg	32 ± 2	31 ± 1	25 ± 1*,+
Endo/epi flow ratio	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
MVL, ml/min/100g	0.03 ± 0.01	0.07 ± 0.01*	0.07 ± 0.02*

*P<0.05, from CONTROL; +P<0.05, from HD.

Title: CONTINUOUS PULSE OXIMETRY IN THE POST-ANESTHESIA CARE UNIT

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Introduction: The early postoperative period is a potentially high risk time for the development of hypoxemia. Consequently, supplemental oxygen is used routinely in the initial post-anesthesia care unit (PACU) stay in many hospitals. For most patients it is later discontinued before discharge to the ward, based on clinical criteria without objective measurement of oxygenation. In this study we monitored a diverse group of adults having general anesthesia for elective inpatient surgery with pulse oximetry continuously throughout their PACU stay. The aims were to examine the: incidence of hypoxemia while on and off oxygen; magnitude of hypoxemia; and relationship to possible associated factors.

Methods: The study was performed in accordance with our institutional review board. Informed consent was obtained from 99 ASA I-III patients who were ≥40 yr old having elective inpatient surgery with general anesthesia (with intubation and positive pressure ventilation). Exclusion criteria were: thoracic, airway, intracranial, major vascular or cardiac surgery; severe cardiorespiratory disease; or anemia. The anesthetic management was at the discretion of the attending anesthesiologist. The PACU staff were blinded to the results unless severe hypoxemia (=hemoglobin saturation ≤90% for ≥2 minutes, or ≤85%, whichever was earlier) occurred. All patients received oxygen by face mask at ≥10 lpm on arrival in the PACU. It was removed after a minimum of 30 min at the nurse's discretion using our usual PACU criteria (awake; normal strength and vital signs). Discharge was also determined by the PACU staff, but required at least 45 min since removing the oxygen. Continuous pulse oximetry (Nellcor N-100) began 5 min after arrival in the PACU and ended at discharge. An investigator constantly observed the hemoglobin saturation (SpO_2) to eliminate artifacts and record the SpO_2 every 5 min and anytime it fell below the preceding 5 min value. The 5 min values were used to calculate the mean SpO_2 and all were used to determine the minimum SpO_2. During hypoxemic episodes (=SpO_2 ≤90% for ≥15 seconds) the respiratory rate (RR), position, minimum SpO_2 and duration were recorded. Oxygen was administered on discharge if it had been resumed due to a severe hypoxemic episode or if, in the 10 min before discharge, a hypoxemic episode occurred or the SpO_2 was generally ≤92%. The night before surgery, 92 subjects had pulse oximetry for 15 min. The SpO_2 was recorded every 1 min and anytime it fell below the preceding 1 min value. The mean was determined from the 1 min values and the minimum using all values. If any preoperative SpO_2 was <91% the patient was excluded. The data are presented as mean±1 SD. Chi-square and Student's t-tests were used where appropriate. P<0.05 was considered significant.

Results: The 99 subjects included 57 females and 42 males, with a mean age of 59±11 yr and % ideal body weight (IBW) of 121±24%. They were studied for 53±28 min on oxygen and 53±27 min off. The mean and minimum SpO_2 preoperatively and while on and off oxygen in the PACU are shown in TABLE 1. The minimum SpO_2 on oxygen occurred at 21±24 min after arrival in the PACU, and the minimum off oxygen was at 81±34 min after arrival and 28±19 min after discontinuing oxygen. At least 1 hypoxemic episode occurred in 38.4% of the subjects, a severe episode in 20.2% and 29.3% received oxygen on discharge. Hypoxemia only occurred while off oxygen. Severe episodes were managed by resuming the oxygen, which corrected the hypoxemia in ≤4 min. For those who desaturated, the number of episodes per patient was 5±5, with mean and maximum durations of 75±44 and 120±94 sec and minimum SpO_2 of 87.4±2%. They began at 84±33 min after entering the PACU and 26±24 min after discontinuing oxygen. Thirty-seven, 53, and 11% of subjects were in the supine, semi-sitting or lateral position, respectively, when hypoxemic. The RR was <10bpm (6-8bpm) in 3 patients when hypoxemic. Cyanosis was noted in only 1 episode. Sixteen patients had mild upper airway obstruction and 3 had Cheyne-Stokes breathing during their hypoxemic episodes. There was no association between the occurrence of ≥1 hypoxemic episode and age (40-63yr = 28/69; ≥65 = 10/30); %IBW (<120% = 18/55; ≥120% = 19/44); smoking (current = 8/14; past = 12/28; never = 18/57); preoperative minimum SpO2 (≥95% = 17/56; <95% = 18/36); premedication (narcotic = 24/56; benzodiazepine= 4/19; none = 10/24); surgery duration (<60min = 4/19; ≥60min = 32/80); or surgical site (upper abdominal = 15/30; lower abdominal = 8/21; peripheral = 15/48). TABLE 2 shows the factors that were associated with hypoxemia.

Discussion: This study confirms the efficacy of supplemental oxygen in the early PACU period. However, after discontinuing oxygen a high percentage of patients had ≥1 episode of hypoxemia. In 20%, the episodes were severe enough to warrant resuming the oxygen. This data is particularly alarming since patients usually considered at risk were excluded from the study and cyanosis was noted in only 1 episode. Our incidence is higher than previous reports[1], possibly due to our: intensive continuous monitoring; blinding of the PACU personnel; and examining only the ≥40 yr age group. The only predictive factors reaching statistical significance were ASA class >I and preoperative mean SpO_2 <95%. We conclude that hypoxemia is a common occurrence in adults after discontinuing oxygen in the PACU and: either all patients should have pulse oximetry for at least 45 min after discontinuing oxygen; or the oxygen should not be removed and all patients should be sent to the ward with supplemental oxygen.

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TABLE 1: Preoperative and PACU SpO_2

	Preoperative	PACU-on O_2	PACU-off O_2
Mean SpO_2(%)	96.2±1.6*	99.5±0.8+	94.8±2.0
Minimum SpO_2(%)	94.9±1.9*	98.6±1.6+	91.3±3.8

O_2 = oxygen mask * p<0.05 vs PACU on and off oxygen
+ p<0.05 vs PACU off oxygen

TABLE 2: Factors Associated with Hypoxemia

ASA Class	I	4/29 (13.8%)*
	II	22/55 (40%)+
	III	12/15 (80%)
Preoperative Mean SpO_2	≥ 95%	25/81 (30.9%)++
	< 95%	9/11 (81.8%)

* p<0.05 vs II,III + p<0.05 vs III ++ p<0.05 vs <95%

TITLE : AIRWAY PRESSURE MONITORING AS AN AID IN THE DIAGNOSIS OF AIR EMBOLISM

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INTRODUCTION : Recently, an anecdotal case report has emphasized the efficacy of continuous airway pressure monitoring for detection of air embolism[1]. In conclusion the authors highlighted that it is a sensitive, safe, simple, noninvasive and cheap method. However, to our knowledge no study has evaluated and compared the airway pressure monitoring with established monitoring aids in a series of patients. This study was designed to examine the validity of airway pressure monitoring with that of end–tidal CO_2($ETCO_2$) monitoring for diagnosis of air embolism.

METHODS : Seventy six patients of either sex undergoing neurosurgical operations in sitting position were studied after obtaining their informed consent and institutional approval. Anesthesia was induced with thiopentone and suxamethonium was used for intubation. Oxygen with N_2O (1:2), pancuronium, narcotic analgesics were used for maintaining anesthesia. IPPV was continued with Air–Shield Ventimeter ventilator^R. $ETCO_2$ was maintained around 30mmHg. CVP catheter was introduced through an antecubital vein. Continuous monitoring of heart rate, ECG, intra–arterial pressure and $ETCO_2$ were carried out in all the patients. Air way pressure was continuously monitored by a technique as described by Baker et al[2]. An air filled Gould transducer was placed externally on the chest at a level of carina. It was connected by a rubber tubing to a side arm port of a 90° angle connector attached to the endotracheal tube. This pressure was displayed on an oscilloscope and recorded along with ECG and blood pressure. All the patients were administered maintenance dose of pancuronium at a regular interval of 30 minutes. This was strictly adhered in order to avoid light plane of anesthesia. A sudden and sustained fall in $ETCO_2$, a sudden rise in air way pressure or any unexplained perturbations in heart rate and arterial pressure were considered as signs of air embolism. The time of onset, stage of surgery and duration of disturbances were recorded. At the same time chest was auscultated for any murmur and aspiration of air was also tried through the CVP catheter for diagnosis and management of air embolism.

RESULTS : In 16 patients 24 episodes of air embolism were observed based on the $ETCO_2$ monitoring criteria. The fall in $ETCO_2$ were in the range of 7–16mmHg from the baseline. It remained low for 6–35 minutes. Tachycardia was observed during 10 episodes in 9 patients out of 16. Hypotension was observed on 9 occasions in 8 of 16 patients. Therapeutic intervention to restore blood pressure to normal level was needed in one patient. Six patients had rise in airway pressure along with fall in $ETCO_2$. This rise was in the range of 4–6mmHg and remained high for 5–10 minutes. However, murmur and aspiration of air were positive in 4 and 6 patients respectively (Fig). Rest of the postoperative period was uneventful.

DISCUSSION : $ETCO_2$ monitoring though, not a highly sensitive method of detecting air embolism still it detects entrainment of air much earlier to hemodynamic disturbances. Incidence of 31.5% in the present series confirms previous observations[3]. Low incidence of positive air retrieval through the CVP catheter may be attributed to malpositioning of the catheter tip[4]. Airway pressure monitoring recognized air embolism only in 7.9% of the patients (Fig). The rise in airway pressure was also marginal (4–6mmHg) which, may be missed during monitoring. It is also a poor predictor of complete resolution of entrapped air.

CONCLUSION : From this study we conclude that continuous airway pressure monitoring is not a sensitive indicator of air embolism. Rather it is inferior to ECG and arterial pressure (AP) monitoring.

This study was supported by AIIMS research grant.

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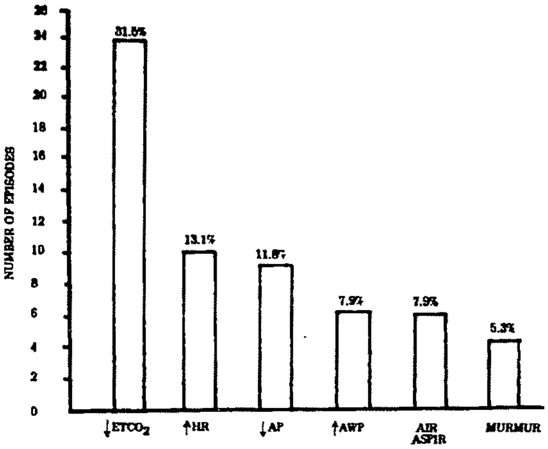

Fig. OBSERVATIONS DURING AIR EMBOLISM

Title: HEMODYNAMIC RESPONSE TO DOBUTAMINE AT DIFFERENT LEVELS OF HALOTHANE ANESTHESIA IN DOGS.

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Introduction. Dobutamine (Db) is a synthetic inotropic agent with beta and alpha-receptor stimulating properties(1). Db-induced improvement in cardiac performance is usually associated with reduction of pulmonary capillary wedge pressure (PCWP) and left ventricular end-diastolic pressure (LVEDP).(2)(5) Yet, substantial elevations of PCWP, of arterial pressure (BP) and episodes of angina have been reported following Db in patients with cardiac failure.[4] Recently, Tarnow[5] reported that the degree of preoperative beta-receptor blockade altered the cardiovascular (CV) response to Db. We investigated here if increasing the depth of halothane anesthesia also could alter the CV response to Db.

Methods. Following approval of the Institutional Animal Care and Use Committee, twelve mongrel dogs, anesthetized with 25 mg/kg pentobarbital, had tracheal intubation and had anesthesia maintained with 50% N_2O in O_2 and 0.4% end-tidal halothane (H) with controlled ventilation. Measurements of left ventricular end-diastolic pressure (LVEDP), peak dP/dt and BP were obtained from 5F Millar catheters introduced by retrograde catheterization of right carotid and femoral arteries. Pulmonary artery pressure (PAP) and CO (thermodilution) were obtained via a 7F Swan-Ganz catheter. Heart rate (HR) was derived from the ECG (lead II). End-tidal halothane concentrations (ETHC) were measured on-line by a piezo-electrical multigas analyzer (EMMA). After control measurements had been obtained at 0.4% ETHC, H was increased to 0.8% ETHC in 6 dogs (Group I) and to 1.6 ETHC in 6 other dogs (Group II) and maintained at that level for 20 min whereafter baseline (B) measurements were made. Then, while still maintaining H anesthesia at these levels, 5-min infusions of 1 (D_1), 2 (D_2), 4 (D_4) and 6 (D_6) mcg/kg/min of Db were given stepwise. CV measurements were made at the end of each Db infusion. Statistical analysis included one- and two-way analysis of variance (ANOVA), Newman-Keuls tests and unpaired Student's t-tests.

Results. Mean values and standard deviations ( ) of CV variables at B and at D_6 are listed in the table. At B, only peak dP/dt was different between the groups (1517 versus 632 mm Hg.sec^{-1} in groups I and II respectively, $p < 0.01$). Db produced overall statistically significant changes in BP, PAP, peak dP/dt, CO and SV in both groups and additional changes in HR, PCWP and LVEDP in Group II only ($P < 0.01$ by ANOVA1R). Treatment with 1.6% ETHC changed the overall Db-induced response of BP ($p < 0.025$), PAP ($p < 0.025$), PCWP ($p < 0.001$), peak dP/dt ($p < 0.001$) and LVEDP ($p < 0.01$) compared to 0.8% ETHC (ANOVA2R).

Discussion. Db improved CO at either ETHC. However, the CO/LVEDP plot (see Figure) shows that whereas the Db-induced increase in CO caused only a mild increase in LVEDP at 0.8% ETHC, LVEDP increased by 140% at 1.6% ETHC. This implies a greater stress on the heart and a reduced cardiac efficiency at 1.6% ETHC. Although we did not study the involved mechanism, a reduction in diastolic compliance is perhaps responsible for this Db-induced severe increase in LVEDP at 1.6% ETHC. In summary, high levels of halothane adversely affect some aspects of the CV response to Db.

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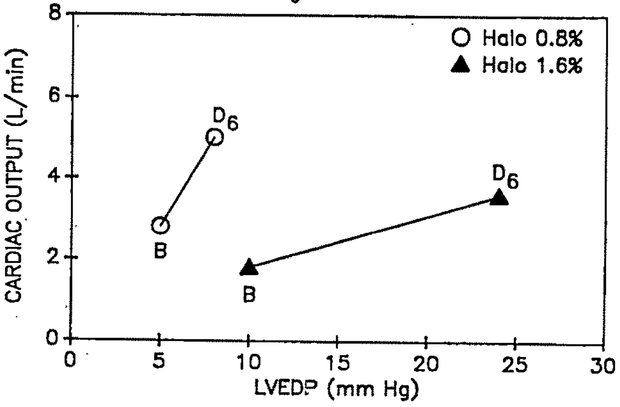
TABLE

	Group I (n = 6)		Group II (n = 6)	
	B	D_6	B	D_6
HR (beats/min)	132(33)	143(39)	112(9)	134(13)
BP (mmHg)	87(32)	108(21)*	71(17)	122(17)#
PAP (mmHg)	12(2)	18(2)#	12(3)	26(8)#
PCWP (mmHg)	6(3)	7(3)	9(4)	19(8)#
dP/dt (mmHg/sec)	1517(651)	3630(1364)#	632(371)	1754(404)#
LVEDP (mmHg)	5(8)	8(5)	10(24)	24(9)#
CO (L/min)	2.8(1.3)	5(2)#	1.8(.5)	3.6(.6)#
SV (cc/beat)	22(10)	34(14)#	16(5)	27(6)#
SVR (Units)	34(14)	27(14)	40(14)	33(5)#

Mean values and standard deviations ( ) of CV variables at baseline (B) and after the last stepwise infusion of dobutamine (D_6) during anesthesia with 0.8% (Group I) and 1.6% (Group II) end-tidal halothane concentration. Statistically significant difference between D_6 and B by Newman-Keuls test: * ($P < 0.05$) and # ($P < 0.01$)

Figure



CO and LVEDP coordinates (n=6, mean values) at baseline (B) and in response to dobutamine (D_6) at 0.8% and 1.6% ETHC (Halo).

Title: CONTINUOUS ALFENTANIL INFUSION IN CHILDREN UNDERGOING GENERAL ANESTHESIA FOR COMPLETE ORAL REHABILITATION PROCEDURES

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Introduction: Alfentanil is a new synthetic congener of fentanyl. It is relatively lipid, insoluble, and highly protein-bound. Its small Vd and short elimination half-life coupled with its large margin of safety and properties of providing hemodynamic stability make it a useful anesthetic agent to be administered either as a bolus injection or as an intermittent infusion. At present, little information is available on the pharmacodynamics of alfentanil in pediatric surgical patients. This study was designed to evaluate the safety and efficacy of a continuous alfentanil infusion in pediatric patients undergoing general anesthesia for complete oral restorative procedures.

Methods: After our Institution's Human Rights Committee approval and the informed written consent of a parent were obtained ASA I and II patients scheduled for elective complete oral restorative procedures under general anesthesia were randomized to one of two groups. Both groups underwent an inhalational induction via face mask with halothane and N_2O/O_2. After venous access was established, atracurium and atropine were administered to facilitate muscle relaxation, prevent chest wall rigidity, and prevent bradycardia. All patients were nasally intubated. In patients in group 1 (n=14), the halothane was discontinued and when the end tidal halothane concentration was less than 0.1%, 100 µg/kg of alfentanil was administered. Three minutes later, a continuous infusion of alfentanil (2 µg/kg/min) was begun. Supplemental bolus injections (10 µg/kg) were given in response to hemodynamic changes greater than 20% above baseline. If three bolus injections were administered, then the infusion was increased by 0.5 µg/kg/min. If hemodynamic stability was maintained for greater than 20 minutes, then the infusion was decreased by 0.5 µg/kg/min. For the patients in group 2 (n=11), the halothane was initially maintained at 1.5% during intubation and initial surgical stimulation and then adjusted to the anesthetic needs of the patients.

Heart rate and blood pressure were recorded on admission to the outpatient surgical facility (T1), arrival in the OR (T2), 1 minute pre- and post-alfentanil (100 µg/kg bolus) injection (T3,4), 1 minute pre- and post-intubation (T5,6), 1 minute pre- and post-surgical stimulation (T7,8), as well as throughout the recovery room stay. In addition to the hemodynamic data, the length of time until extubation and alertness (the time the last gas was discontinued until the time the patient was extubated or alert) were recorded. In the recovery room the need for postoperative pain medication was recorded as well as the incidence of vomiting. Statistical analysis included repeated measures analysis of variance, Fischer exact test, and unpaired student t test; statistical significance was considered for $p < 0.05$.

Results: There were no significant differences between the groups with respect to weight and age, duration of surgery, or anesthesia. The mean ± SD dose for alfentanil was 2.6 ± 0.6 µg/kg/min. Compared with hemodynamic measurements at T3 (i.e., time period following atropine administration but prior to alfentanil injection) for the alfentanil group, systolic blood pressure was significantly different at T6, T7, and T8. While for patients anesthetized with halothane systolic blood pressure was significantly different at T6. There were no significant changes in heart rate with time following atropine administration in either group. At the conclusion of the anesthetic, the time from when the last anesthetic gas was discontinued until the time the trachea was extubated (4.0 ± 2.0 min vs 10.5 ± 5.4 min) and the time the patient was alert and responsive (10.4 ± 9.1 min vs 37.0 ± 17.2 min) were significantly shorter in the alfentanil group. There was no postoperative respiratory depression in either group. Although the incidences of nausea and vomiting in the recovery room for the halothane group was none and in the alfentanil group was 2 of 14 patients, these differences were not statistically significant.

Discussion: Inhalational anesthetics, in particular halothane, have served as the anesthetic agent in children. Alfentanil, a highly protein-bound and less lipid, soluble congener of fentanyl, has a small Vd and short elimination half-life. In children its pharmacokinetic properties make it a useful intravenous agent which can be administered either as a continuous intravenous infusion or as a bolus injection. We evaluated the safety and efficacy of continuous alfentanil infusion in children undergoing dental surgery. Although systolic blood pressure was statistically higher during the stress periods of surgery and anesthesia and pre- and post-stimulation, these values were within clinically-acceptable ranges. When compared to halothane, patients anesthetized with alfentanil had shorter times until extubation and shorter times until alertness. We feel that in children continuous infusion alfentanil is safe and efficacious.

*Supported in part by Janssen Research Foundation.

	ALF HR	HAL HR	ALF SYS BP	HAL SYS BP
T_1	106 ± 22	112 ± 10	95 ± 13	98 ± 12
T_2	115 ± 31	129 ± 19	110 ± 18	110 ± 20
T_3	131 ± 23	143 ± 24	100 ± 8	94 ± 12
T_4	124 ± 24	151 ± 11	94 ± 9	96 ± 10
T_5	127 ± 23	151 ± 11	96 ± 9	94 ± 9
T_6	146 ± 26	159 ± 9	109 ± 13*	108 ± 13*
T_7	123 ± 40	148 ± 10	110 ± 12*	93 ± 9
T_8	134 ± 27	147 ± 9	112 ± 12*	94 ± 8

* $p < 0.5$ compared with values at T_3.

Title:
REVERSAL OF MALIGNANT HYPERTHERMIA EPISODES BY AZUMOLENE IN SUSCEPTIBLE SWINE

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Introduction: Azumolene, 1-[[[5-(4-bromophenyl)-2-oxazolyl]-methylene]amino]-2,4-imidazolidinedione, is an analogue of dantrolene with the useful property of much greater water solubility.

Azumolene has been found to have similar effects to dantrolene on muscle tissue obtained from individuals susceptible to malignant hyperthermia (MH). Allen, et al. measured the intracellular calcium concentration *in vivo* in muscle cells from MH-susceptible swine. They found that azumolene caused a dose-dependent decrease in the intracellular calcium concentration in doses from 0.5-2.0 mg/kg [1]. Fletcher, et al. studied the effects of azumolene on strips of human muscle obtained from MH-susceptible patients. They found that azumolene antagonized contractures caused by caffeine to the same degree as dantrolene when the drugs were used at the same concentration (10 μM) [2].

The purpose of the present study was to determine if azumolene could reverse clinical episodes of MH in susceptible swine.

Methods: The study was approved by the Subcommittee on Animal Care of the Massachusetts General Hospital. A herd of Pietrain pigs, inbred for susceptibility to MH, was maintained at the research farm of the Boston Biomedical Research Institute and fed commercial pig chow ad libitum. Offspring of sows and boars known to be susceptible to MH were weaned at age 6-8 weeks.

Azumolene was provided by Norwich Eaton Pharmaceuticals. An isotonic solution of azumolene was prepared using guidelines provided by the manufacturer, and contained azumolene 10 mg/ml, glycerol 2.2% v/v, and potassium hydroxide to adjust the pH to 10.2.

For determination of MH susceptibility, the following procedure was employed. The pig was given ketamine, 10 mg/kg, via an intramuscular injection in the rump. After approximately 10 min, a 22-24 gauge Teflon intravenous catheter was inserted into an ear vein without complaint from the pig, a normal saline infusion begun, and ECG leads applied. The pig was then given 2% halothane and 67% nitrous oxide in oxygen by an anesthesia face mask, allowed to breathe spontaneously, and observed for signs of MH. Minute ventilation was measured with a Wright spirometer, and temperature was determined with a rectal thermistor.

Susceptibility to MH was assessed on the basis of the following clinical criteria: Swine responsive to halothane and therefore positive for MH became tachycardic, tachypneic, and manifested rigidity of the hind limbs while breathing halothane. Typically their minute ventilation increased threefold in comparison to that measured during ketamine sedation. Temperature did not change during the short course of these experiments because the halothane was discontinued and the animals were treated with azumolene as soon as muscle rigidity was apparent. Swine nonresponsive to halothane and therefore presumably negative for MH hypoventilated to the point of apnea while breathing 2% halothane and did not manifest hind limb rigidity.

Once the diagnosis of MH had been made, the pig was given 100% oxygen by mask and azumolene intravenously in 5 mg increments, waiting 2 min between doses, until the hind limbs were supple. The pigs were allowed to recover and returned to the farm.

Results: Azumolene was administered to ten MH-susceptible swine after they had been triggered into an MH episode via the inhalation of halothane. In each case, the episode was terminated by a dose of azumolene less than 2 mg/kg. There was an inverse relationship between the time required for development of hind limb rigidity and the total dose of azumolene required to reverse such rigidity. Thus, swine which are more sensitive to the triggering effect of halothane (and which more quickly manifest the signs of MH) require a larger dose of azumolene to reverse the MH episode. This relationship is shown in Figure 1.

Discussion: The major disadvantage to the use of dantrolene during an episode of MH is its lack of water solubility and difficulty in preparing a solution suitable for intravenous administration. Indeed, Gronert has stated that the process of preparing dantrolene solutions during an MH crisis "will require the full time efforts of three or four people." In addition, the solutions may need to be heated to facilitate dissolution, or administered through a blood component filter in order to remove undissolved drug [3].

Azumolene may represent a significant improvement in the therapy of MH. Its solubility of 10 mg/ml in an isotonic solution, in comparison to that of dantrolene in a hypertonic mannitol solution (0.33 mg/ml), means that a therapeutic dose may be administered employing one-thirtieth the volume. Thus, a 70 kg patient who required 2 mg/kg of drug to reverse an MH episode could have the total dose of azumolene contained in two 10 ml syringes, in contrast to dantrolene contained in seven 60 ml syringes, saving much critical time.

The data in Figure 1 show that the ED50 for azumolene is approximately 0.85 mg/kg. In our experience with our herd of MH-susceptible swine, we have used an initial dantrolene dosage of 1 mg/kg, and repeated this dose if necessary to terminate an MH episode. Using dantrolene to terminate nearly one hundred episodes of MH, we have found that a dose of 1 mg/kg was effective in approximately 80% of the pigs, while the remainder had their episodes reversed by a dose of 2 mg/kg. Therefore, azumolene appears to be approximately equipotent with dantrolene in terms of reversal of MH episodes, in agreement with previous studies comparing physiological effects of the two drugs [1-2].

Further studies are needed on the toxicity of the drug in laboratory animals and on the stability of the drug in solution. Based on the results of such studies, azumolene may be a candidate for studies in human MH.

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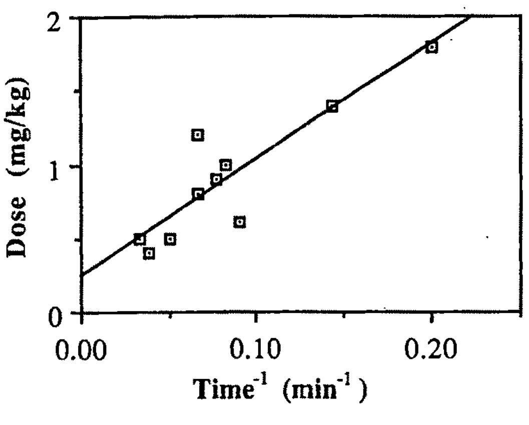

Figure 1

Title: USE OF AN OXYGEN CONCENTRATOR AS THE GAS SOURCE FOR GENERAL ANESTHESIA

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Introduction. Compressed oxygen is an integral part of inhalational general anesthesia as taught and practiced in the USA.

This requirement may present a major hinderance when anesthetics have to be given under adverse conditions, as oxygen cylinders may not always be readily available, such as during military anesthesia "in the field" or after catastrophic civil disruptions. However, with the advent of portable and reliable gas powered electric generators, the availability of electricity is almost ubiquitous. We developed a portable anesthesia system using a disposable anesthesia circuit and an electrically driven oxygen concentrator which extracts oxygen from air. We now report on the use of this apparatus in providing general inhalational anesthesia to patients undergoing surgery in a standard operating room.

Methods. The anesthetic system consisted of a MiniO2 (TM) oxygen concentrator (Mountain Medical Equipment, Inc.), capable of supplying up to 5 l of 85% oxygen per minute, connected to a portable circle system (DISP CO2 SORB (TM) , Dryden Corporation) via a calibrated vaporizer (Ohio Medical Products) specific for isoflurane. Informed consent from 12 patients and institutional approval were obtained. The usual patient monitors were applied. Anesthesia was induced with thiopental 3-5 mg/kg and continued with isoflurane and oxygen, delivered either through a mask or tracheal tube. When necessary, opioids and muscle relaxants were given intravenously. Patients either breathed spontaneously or their lungs were ventilated manually. A fresh gas flow of 4 l/min was used for the first 5 - 10 minutes of anesthesia, followed by flows of 0.5 - 1.0 l/min for the duration of the case. We recorded the patients' age, sex, physical status, weight and height, the surgical procedure, duration of anesthesia, time to awakening from the end of the surgical procedure, and the occurrence of any problems encountered with maintaining adequate oxygenation or ventilation. An overall clinical impression of the anesthetic apparatus was then made.

Results. Patients' ages ranged from 4 to 72 years; their ASA status ranged from 1 to 3. The duration of surgical procedures ranged from 30 minutes for a laparoscopy to 5 hours for a bowel resection. The in-circuit FIO2 never decreased below 0.75. All patients were responding to verbal commands within 10 minutes from the end of surgery, and no problems were encountered with the apparatus except for the noise produced by the oxygen concentrator, which disturbed some surgeons. The anesthesiologist's overall clinical impression of the system was very favorable.

Discussion. Oxygen concentrators are being increasingly used to supply medical oxygen in hospitals and in the home.(1) A zeolithic molecular sieve is used to separate oxygen from nitrogen. Argon, having a similar affinity as oxygen for zeolite, is also concentrated five fold, to a maximum of 5% (2). However, accumulation of argon in the anesthetic circuit is insignificant when fresh gas flows above 0.5 l/m are used.(3) The noise problem was solved, when necessary, by moving the oxygen concentrator outside of the O.R. door and using plastic tubing to convey the gas to the vaporizer and CO2 absorber, which remained at the head of the table. The entire apparatus weighed only 28 kgs, making it suitable for use "in the field". Other portable anesthetic systems have been described based on drawover systems (4) as well as total intravenous anesthesia (5). However, with the drawover apparatus, in order to achieve a high FIO2, which may be indicated in some situations such as with chest injuries, large quantities of compressed oxygen are required. Total intravenous anesthesia, although especially portable, demands the use of several drugs which may not be readily available under adverse conditions.

We have described a system for general inhalational anesthesia that is portable and easy to use, operates without pressurized gases and provides a high FIO2 with a practically limitless supply of oxygen.

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Title: PATCH-CLAMP ANALYSIS OF SUCCINYLCHOLINE ACTION AT THE ACETYLCHOLINE RECEPTOR CHANNEL

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Introduction: We have previously claimed (1) that succinylcholine (SCh) activates the acetylcholine (ACh) receptor channel in a manner similar, but not identical, to its activation by the native agonist acetylcholine. Specifically, we showed that succinylcholine opens a channel having a conductance of 43 pS, similar to that of the channel activated by acetylcholine, but that the mean duration of openings triggered by succinylcholine was briefer than those triggered by acetylcholine. These conclusions were drawn on the basis of the steady-state behavior of channels in the presence of relatively high concentrations of agonist; conditions under which the role of receptor desensitization could not be adequately assessed. We have now extended these studies by measuring the response of acetylcholine receptor channels to a wide range of agonist concentrations and by using a rapid perfusion method (2) to circumvent the problem of desensitization.

Methods: BC3H-1 cells, which express nicotinic acetylcholine receptor channels similar to those of the human neuromuscular junction, were grown in culture and prepared for electrophysiological recording (3). Outside-out membrane patches (4) were formed at the tips of glass micropipettes and were positioned within a stream of flowing solution which contained no agonist. A solenoid-driven pinch valve was used to make timed, rapid applications of acetylcholine or succinylcholine. Each agonist application resulted in an abrupt increase in current flowing across the membrane patch, followed by a dose- and agonist-dependent decrease due to desensitization. For experiments carried out at steady state (where individual ion channel events could be resolved), the mean of 100-500 open channel durations was calculated.

Results: Table One displays the quantitative features of the steady-state kinetic behavior of ACh receptor ion channels in the presence of a low concentration (200 nM) of SCh and ACh. Channel openings activated by SCh tend to be briefer and less frequent.

TABLE ONE

Patch	ACh MOT	SCh MOT	Difference (%)	ACh events/s	SCh events/s
1	3.69	2.44	34	14	10
2	3.79	2.21	42	99	11
3	3.39	2.52	26	15	<1
Mean	3.62	2.39*	34		
SD	0.21	0.16			

MOT = mean open time in milliseconds at -100 mV
*significantly different from ACh MOT (p = 0.027)

Figure One illustrates the response of a membrane patch to 200-ms applications of high (saturating) concentrations of the two agonists. The larger, more rapidly decaying signal is the mean of 13 applications of 100 μM acetylcholine; the smaller, more slowly decaying signal is the mean of 19 applications of 1000 μM succinylcholine. A dose-reponse curve, compiled from the responses of two membrane patches exposed to a range of concentrations of succinylcholine, is presented in Figure Two. The ACh dose-response curve (5) is shown for comparison.

FIGURE ONE

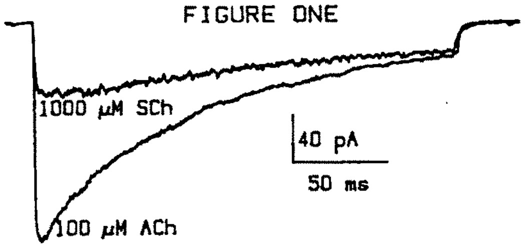
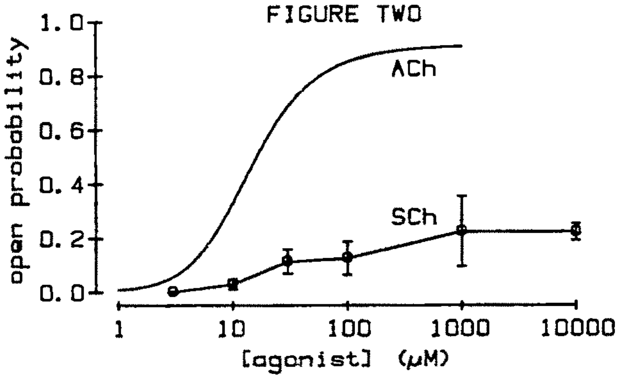


FIGURE TWO



Discussion: Succinylcholine exhibits the classic profile of a partial agonist: even at high concentrations, it can open only a small fraction of the ion channels normally activated by acetylcholine. This behavior arises from two features of its action at the level of individual ion channels: first, the SCh-bound ion channel has a smaller probability of opening than the ACh-bound ion channel. Second, the SCh-bound channel, once open, has a higher probability of closing than the ACh-bound channel. These results, if generalizable to human nicotinic acetylcholine receptor channels, imply that full paralysis by succinylcholine occurs when a relatively small fraction of the available receptor channels are open.

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Title: EVALUATION OF OXYGEN SATURATION (SpO_2) MONITORING BY PULSE OXIMETRY IN NEONATES IN THE DELIVERY ROOM

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Introduction: Studies in neonatal intensive care units have demonstrated a good correlation between values of saturation from pulse oximetry (SpO_2) with those from arterial blood sampling (SaO_2) [1]. Harris et al [2] used the pulse oximeter in the delivery room to measure SpO_2 in newborns (NB) by applying a sensor over the Achilles tendon and found that they remained relatively desaturated in the immediate postpartum period. It was concluded that careful monitoring of neonatal oxygenation in the delivery room, even after normal delivery, may be warranted. However, it is well documented that in the immediate postpartum period, R-L shunting of venous blood through the ductus arteriosus may persist, producing low SaO_2 in lower extremities, compared to a much higher SaO_2 in the upper part of the body. Therefore, SaO_2 obtained from the Achilles tendon may not represent the "normal" values of SaO_2 in blood perfusing the brain and heart. The present study was designed to evaluate SaO_2 in the NB by simultaneously placing pulse oximeter sensors over the ulnar side of the (R) hand and (R) Achilles tendon. The purpose of this investigation was to determine whether there is a significant difference in SpO_2 between these two locations and, if so, to advise which one should be used routinely in the delivery room.

Methods: This study was approved by the Human Investigation Committee of our institution and informed consent was obtained from each mother. One hundred NB delivered vaginally (n=63) or by Cesarean section (n=37) with general or regional anesthesia were studied. All mothers, before Cesarean section, received oxygen by face mask. The pediatricians provided postpartum care and assigned an Apgar score at 1 and 5 min. Immediately after clamping of the umbilical cord, pulse oximeter sensors (Model 3700 Ohmeda) were simultaneously placed over the ulnar side of the NB (R) hand and over the (R) Achilles tendon. The SpO_2 was recorded at 1, 5, and 10 min and 24 hours post delivery. Data was analyzed using t-test, with $p<0.05$ considered statistically significant. Data is reported as mean values ± S.D.

Results: Data is presented in the Table. Initial values were obtained within 1 minute in 75% of the NB, within 5 minutes in 98%, and after that, in all NB. At 1 and 5 minutes, SpO_2 recorded on the (R) hand was signficantly higher than SpO_2 recorded from the lower extremity (Table). At 10 minutes, these differences diminished and almost completely disappeared after 24 hours. SpO_2 did not differ significantly between NB delivered vaginally or by Cesarean section, regardless of anesthesia used. Apgar scores at 1 and 5 minutes were all between 6 and 10. In our study, Apgar score for color of the NB, as an objective indicator of oxygenation, did not correlate well with the values of SpO_2 whether from (R) ulnar or (R) Achilles tendon sensing sites. Airway suction of several NB resulted in a drastic reduction in SpO_2 which was promptly reversed by increase in inspired oxygen concentration.

Discussion: Our data confirmed that NB remain relatively desaturated in the immediate postpartum period but with steady improvement of SpO_2 toward normal infant values during the first 24 hours. This early desaturation is a product of right-to-left shunting and significant ventilation/perfusion mismatching. To obtain SpO_2 in immediate postpartum period, pulse oximeter sensor should be placed over right ulnar region of the NB. Thus, the SpO_2 will reflect oxygenation of the brain and the heart. Pulse oximetry is applicable to the NB in the delivery room and can be a useful objective addition to the subjective evaluation of the NB at birth.

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Table:

TIME AFTER DELIVERY

Sensing Site	1 min	5 min	10 min	24 hr	
R hand	71.9±6.5*	83.3±4.2*	90.7±4.6	95.7±2.2	SpO_2 %
R leg	63.4±4.3*	76.6±4.1*	87.1±5.7	95.2±2.3	

* $p<0.05$ between sites

Title: EFFECT OF SODIUM BICARBONATE ON PAIN WITH SKIN INFILTRATION AND ON LOCAL ANESTHETIC STABILITY

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Introduction Local anesthetic agents produce varying degrees of pain on skin infiltration (1). The addition of sodium bicarbonate ($NaHCO_3$) to lidocaine attenuates the pain associated with skin infiltration (2). This randomized and double-blind study was undertaken to determine the relationship of increasing pH and pain with intradermal injections of bupivacaine (BUP) and mepivacaine (MEP) with or without epinephrine (EPI). We also examined the stability of pH-adjusted local anesthetic solutions over time.

Methods After receiving approval from the Institutional Review Board, twenty healthy consenting volunteers were entered into the BUP portion of the study and an additional twenty paid volunteers into the MEP study. For the BUP study, five injections were given: 1) preservative-free normal saline (NS); 2) 0.5% BUP; 3) 0.5% BUP + $NaHCO_3$; 4) 0.5% BUP + EPI; and 5) 0.5% BUP + EPI + $NaHCO_3$.

To alkalinize the BUP, 0.1 ml of $NaHCO_3$ (1 mEq/ml) was added to 10 ml of BUP (3). EPI containing solutions were made by adding 0.05 ml of a 1:1000 solution to 10 ml of local anesthetic solution.

For the MEP study, subjects were also given five injections: 1) preservative-free normal saline (NS); 2) 1.0% MEP; 3) 1.0% MEP + $NaHCO_3$; 4) 1.0% MEP + EPI; and 5) 1.0% MEP + EPI + $NaHCO_3$. The MEP was alkalinized by adding 1.0 ml of $NaHCO_3$ (1 mEq/ml) to 9 ml of MEP. EPI containing solutions were made by adding 0.05 ml of a 1:1000 solution to the local anesthetic solution.

pH values were measured in triplicate with an accuracy of ±0.05. The pH meter was standardized prior to each set of measurements with standard solutions at pH 4.0 and 7.0. $NaHCO_3$ was added in a similar fashion to lidocaine (LID) and to 2 chloroprocaine (CHL) and pH measurements were taken over 30 hours.

Five areas of the volar surface of the left arm were used. Injections were administered randomly and consisted of 0.1 ml injected intradermally followed by 0.2 ml given subcutaneously via a 25 gauge hypodermic needle approximately 15 seconds apart. Following each injection, subjects were instructed to score their pain on a 10 cm linear visual analogue scale (4). Following all of the injections they were then instructed to rank each injection from least to most painful.

Results BUP and BUP + EPI had the highest mean pain scores of 55.8 ± 20 and 54.7 ± 24 respectively. The remaining solutions had the following scores: BUP + $NaHCO_3$ 45.0 ± 22; BUP + EPI + $NaHCO_3$ 35.6 ± 23; NS 29.8 ± 23. Analysis of variance showed a significant non-random distribution among the 5 agents with a P value of $< .001$. BUP + EPI was the most painful in 8 out of 20 subjects and BUP the most painful in 6 out of 20 subjects. The addition of $NaHCO_3$ to BUP + EPI resulted in a 35% reduction in the mean pain score. Significant results are listed in Table 1. No significant differences were found between BUP and BUP + EPI or between BUP and BUP + $NaHCO_3$.

Plain MEP had the highest mean pain score of 49.4 ± 21. The remaining solutions had the following mean scores: MEP + EPI 46.6 ± 21; NS 45.1 ± 23; MEP + $NaHCO_3$ 22.0 ± 23; and MEP + EPI + $NaHCO_3$ 16.2 ± 18. The addition of $NaHCO_3$ to MEP and MEP + EPI resulted in a significant reduction of 55% and 65% in mean pain scores respectively. Significant results are listed in Table 1. No significant differences were found between MEP + $NaHCO_3$ and MEP + EPI + $NaHCO_3$.

All of the local anesthetic solutions maintained a stable pH for at least six hours. There were slight increases in pH in the MEP, MEP + EPI, and LID solutions at six hours. At thirty hours, there was noticeable precipitation in the BUP solutions and crystal formation in the LID solutions. CHL was stable over 30 hours (Table 2).

Discussion This study demonstrates that the addition of $NaHCO_3$ to MEP, MEP + EPI, and BUP + EPI resulted in significant attenuation in pain. We found no significant difference between BUP and BUP + $NaHCO_3$. The addition of $NaHCO_3$ to MEP and to epinephrine containing solutions of MEP and BUP is recommended to diminish the pain of injection.

The addition of $NaHCO_3$ to local anesthetic solutions resulted in an increase in the pH that was stable for at least six hours in all cases and up to ten hours in some cases. However, marked physical changes were evident with BUP and with LID by 30 hours.

TABLE 1
Significant P Values for Paired Comparisons of Mepivacaine and Bupivacaine Solutions

	NS	MEP	MEP+EPI	BUP+EPI+$NaHCO_3$	BUP
BUP+EPI	.0025	-	-	.009	ns
MEP+$NaHCO_3$	.02	.02	.02	-	-
MEP+EPI+$NaHCO_3$	.02	.02	.02	-	-

TABLE 2
pH of Local Anesthetic Solutions with $NaHCO_3$ Measured Over Time

	0	1 h	2 h	3 h	4 h	6 h	10 h	30 h
BUP+$NaHCO_3$	7.0	6.9	6.9	6.8	6.9	6.8	7.0	6.6*
BUP+EPI+$NaHCO_3$	6.9	6.8	6.9	6.8	6.8	6.8	6.8	6.6*
MEP+$NaHCO_3$	7.2	7.3	7.4	7.4	7.4	7.6	7.5	7.6
MEP+EPI+$NaHCO_3$	7.4	7.3	7.4	7.4	7.4	7.6	7.6	7.7
LID+$NaHCO_3$	7.4	7.4	7.4	7.4	7.5	7.6	7.6	7.7+
LID+EPI+$NaHCO_3$	7.5	7.5	7.6	7.6	7.6	7.7	7.8	7.8+
CHL+$NaHCO_3$	7.7	7.7	7.8	7.7	7.7	7.8	7.8	7.8
CHL+EPI+$NaHCO_3$	7.7	7.7	7.8	7.8	7.8	7.8	7.8	8.0

*Precipitate present
+Crystal formation

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THE EFFECT OF ISOFLURANE (1MAC) ON THE NORMAL AV CONDUCTION SYSTEM AND ACCESSORY PATHWAYS

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INTRODUCTION: Halogenated anesthetics can cause significant alterations in heart rate and rhythm. Many investigations have been carried out in animals to assess the effect of inhalational anesthetics on the atrioventricular conduction system (A-V). However, the data from human studies are difficult to interpret because of the lack of similarity among the patient groups, surgical procedures, anesthetic techniques and metabolic conditions during operations.[1] The purpose of this study was to investigate the effect of Isoflurane on electrophysiologic (EP) properties of the normal A-V conduction system and also on accessory pathways in the similar group of patients with Wolf-Parkinson-White (WPW) syndrome during cryoablation of accessory pathways.

METHODS : Following approval from the institutional committee on human research 7 patients 4 women and 3 men with WPW syndrome, aged 21-46, were investigated. All patients were healthy. All of them had pre-operative electrophysiologic studies done. Patients were premedicated with lorazepam 0.06 mg.kg P.O., and morphine 0.1 mg.kg IV. Anesthesia was induced with sufentanil 20 mcg/kg and vecuronium 20 mg·. All patients were monitored with an arterial line, CVP catheter, pulse oxometer, end-tidal capnography (E_tCO_2), and temperature. To monitor depth of anesthesia a halogenated agent monitor (anesthetic agent monitor 222, Puritan Bennett) was used. After sternotomy a baseline electrophysiologic study using epicardial hexapolar electrodes measured:
1) right atrial refractory period (RARP) at cycle length 500 msec and 400 msec [including atrial effective refractory period (AERP), atrioventricular effective refractory period (AVERP), and accessory pathway (APERP)] with coupling intervals in steps of 20 msec (300-400) and 10 msec below 300 msec.
2) right ventricular effective refractory period (RVERP) at cycle length 400 msec. and retrograde accessory pathway refractory period (APERP) and
3) shortest cycle length with 1:1 conduction (SCL). Isoflurane was then administered to the level of 1.4 E_t Volume % and after equilibrium was achieved the above stimulation protocol was repeated. Paired T-test ($p<0.05$) for significance was used to analyze data.

RESULTS: Arterial blood gases, electrolytes and E_tCO_2 were within normal limits. Significant ($p<0.05$) prologations of conduction during 1 MAC Isoflurane were found for antegrade conduction, at cycle length 500 msec. for AERP and for retrograde conduction, at cycle length 400 msec for RVERP and SCL with 1:1 conduction for accessory pathway. (See table).

DISCUSSION: In this homgenous group of patients a significant prolongation in both the normal conduction system and accessory pathway was found duing 1 MAC Isoflurane anesthesia. We were not able to show statistically significant changes within AV-nodal conduction although a trend towards prolongation occurred. These results are similar to other studies, in animals[2], but the effect of Isoflurane on accessory pathways has not been previously reported.

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THE EFFECT OF ISOFLURANE (1MAC) ON THE NORMAL AV CONDUCTION SYSTEM AND ACCESSORY PATHWAYS

C = control
I = 1MAC Isoflurane
ø = p <0.05

ANTEGRADE CONDUCTION								
	AERP		AVNERP		APERP		SCL	
CYCLE LENGTH	C	I	C	I	C	I	C	I
500 msec.	228.14 ±31.14	252.34ø ±29.49	280.42 ±38.7	302.00 ±66.48	220.13 ±31.62	244.36 ±48.03	293.33 ±33.86	321.66 ±37.76
400 msec.	232.11 ±38.06	249.00 ±26.32	264.00 ±40.01	286.14 ±46.18	250.12 ±26.18	268.00 ±42.64	284.14 ±36.44	300.48 ±42.14

RETROGRADE CONDUCTION						
	APERP		VERP		SCL (AP)	
CYCLE LENGTH	C	I	C	I	C	I
400 msec.	213.33 ±32.65	260.01 ±38.92	195.71 ±13.97	224.28ø ±27.60	298.00 ±33.46	334.00ø ±40.09

Title: COMPARATIVE EFFECTS OF VOLATILE ANESTHETICS ON THE SYMPATHETIC ACTIVITY TO ACUTE HYPOXEMIA OR HYPERCARBIA IN DOGS

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Introduction. Either hypoxemia or hypercarbia produces a significant change in the autonomic nervous activity. However, the effects of anesthesia on the nature of the hypoxemia- or hypercarbia-induced sympathetic response still remain unclear. To answer this, we analyzed the threshold response and the gain of the cervical sympathetic activity (CSA) as a function of arterial oxygen saturation (Sao_2)and endtidal carbon dioxide concentration ($FETco_2$). The effects of four volatile anesthetics on CSA during either hypoxemia or hypercarbia were evaluated.

Methods. Fourty eight mongrel dogs were divided into four groups of halothane (H), enflurane (E), isoflurane (I) and sevoflurane (S). They were anestized with thiamylal i.v., intubated and ventilated. Anesthesia was maintained with i.v. infusion of ketamine 0.5mg/kg/hr which does not influence CSA[1]. ECG, arterial blood pressure (ABP) and EEG were continuously monitored. The vagosympathetic trunk was cut free of the surrounding tissues in the neck. The vagus nerve was cut bilaterally to prevent baroreceptor reflex. The sympathetic nerve was cut and desheathed under a microscope. The central cut end was placed on a silver-wire electrode and immersed in a mineral oil pool. Full-wave rectification and area integration of the compound action potentials were performed to obtain the continuous change of CSA as per cent value of the control level[1]. Sao_2 and $FETco_2$ were monitored by fiberoptic oxymetry and capnography. All variables were A/D converted and fed into a HP9816S computer for an on-line real time analysis. Hypoxemia was induced by adding nitrogen to the inspired gas and Sao_2 was gradually decreased to 10%. Hypercarbia was induced by adding carbon dioxide and $FETco_2$ was increased to 10%. The animal was kept constant for 3 min in either condition and then oxygen was inspired again. After the control measurement, the effect of each anesthetic was evaluated at the different concentrations. The study was approved by our Univ. Animal Investigation Committee.

Results. ABP and heart rate increased markedly in response to transient hypoxemia, while they changed less remarkably against hypercarbia. Circulatory responses were tightly coupled with vigorous CSA augumentation, which usually reached 170-220% of the control level in the hypoxemic study and 120-150% in the hypercarbic one. Tonic CSA was differently depressed by the equipotent concentrations of 4 volatile anesthetics.

As CSA increased linearly with decreases of Sao_2, the thresholod (Sao_2 at which CSA rises more than 3% above the tonic CSA level) and the gain (maximum CSA increment divided by the maximum Sao_2 span) were determined. The threshold and the gain were 92% and -1.88 without anesthetics. They were 89% and -1.16 for H, 81% and 0.74 for E, 84% and -1.16 for I, and 86% and -0.94 for S at 1MAC, respectively (Fig.). The maximum CSA response to acute hypercarbia was 130 % of the control level without anesthetics. It was suppressed to 112%, 104%, 122%, and 117% in the presence of 1MAC of H, E, I and S, respectively.

Discussion. CSA augumentation responding to acute hypoxemia was more pronounced than that to acute hypercarbia. The different site and sensitivity of the chemoreceptors might be responsible to the diverse effects of hypoxemia or hypercarbia. Since denervation of the carotid sinus nerves diminished hypoxemic CSA response, the central reflex pathway might control the threshold and the gain of CSA against hypoxemia. EEG activities showed prominent changes under progressive hypoxemia and when it became isoelectrical, it was coincided with an abrupt break of the strained CSA. This seemed to cause the circulatory collapse.

Conclusion. It is concluded that the suppression of autonomic regulations under hypoxemia or hypercarbia are the most prominent with enflurane anesthesia. And it is suggested that volatile anesthetics can cause diminished autonomic nervous system regulation against either hypoxemia or hypercarbia, and make the manifestation of clinical signs of hypoxemia or hypercarbia retarded.

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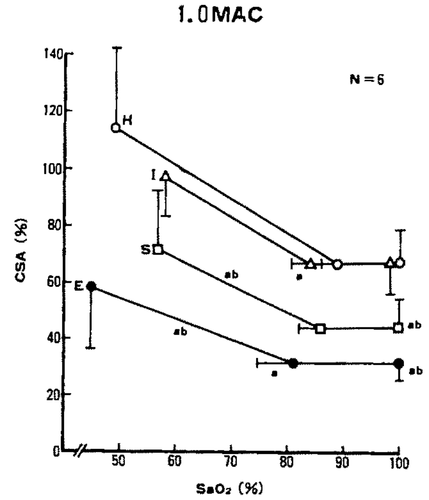

Fig. Comparative effects of 1MAC of halothane, enflurane, isoflurane and sevoflurane on CSA during transient hypoxemia.
a: $p<0.05$ vs halothane, b: $p<0.05$ vs isoflurane

Title:

EVALUATION OF A 28 GAUGE CATHETER FOR CONTINUOUS SPINAL ANESTHESIA

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Introduction:

Continuous spinal anesthesia (CSA) has the following advantages in comparison to a single injection technique: 1) The duration of anesthesia can be controlled through the use of incremental doses of short-acting local anesthetics; this allows for maintenance of anesthesia during long cases, and permits rapid recovery following the completion of surgery. 2) There is greater control over the extent of the spinal block, resulting in a decreased incidence of hypotension.[1] 3) Increased safety can result from the ability to position the patient prior to activation of the block.

Despite these apparent benefits, the significant risk of post dural puncture headache associated with the relatively large bore catheters that are currently available has severely restricted the use of this technique. The present study was conducted to examine the feasibility of using a smaller catheter, sized to pass through a standard 22 gauge needle, for performance of CSA.

Methods:

Following approval from the University of California, San Francisco Committee on Human Research, and after obtaining written informed consent, 30 patients scheduled for surgery involving the lower abdomen, pelvis, or lower extremity were studied. Criteria for exclusion from the study included a significant history of back pain, prior lumbar laminectomy, evidence of abnormal coagulation, or a history of chronic or severe headaches. Premedication, monitoring and administration of supplementary sedatives, analgesics and/or anesthetics were left to the discretion of anesthetist caring for the patient. Continuous spinal anesthesia was established using the following technique. The lower back was widely prepped with Betadine solution. Using sterile technique, a skin wheal was made using 1% lidocaine in an interspace L2-3 or below. A standard 22 gauge 3.5" spinal needle (B-D) was inserted through the anesthetized skin and advanced until free flowing CSF was obtained. A small plastic introducer was placed in the hub of the spinal needle to facilitate insertion, and a 28 gauge radiopaque spinal catheter with a stylet recessed 2.5 cm from the tip (Kendall R&D) was advanced 4-5 cm into the subarachnoid space. The needle was withdrawn, the stylet was removed, and the catheter was taped to the skin. Prior to initiation of the block, an attempt was made to aspirate CSF through the catheter. Incremental doses of local anesthetic were administered to achieve a level sufficient for performance of the proposed surgery; additional doses were given as needed throughout the case. At the end of surgery, the catheter was withdrawn and checked for integrity. Postoperatively, patients were monitored in the Post Anesthesia Care Unit (PACU) for return of motor, sensory, and proprioceptive function. An attempt was made to contact all patients on postoperative days 1 and 7; they were specifically questioned regarding possible complications including post dural puncture headache. To compare the function of this catheter with the catheter we have routinely used for CSA (Burron Perifix® 18 gauge compatible epidural catheter) the charts from 28 patients that had surgery in a similar anatomic location performed under CSA were retrospectively reviewed. Differences between the two groups were determined using unpaired *t* -tests, with $p<0.05$ considered significant.

Results:

Of the 30 patients studied to date, 18 were male and 12 were female; this included 2 patients, one male and one female, that were each studied twice. Their ages ranged from 23 to 90, with an average age (± SD) of 59 years (± 16.3). Catheters were successfully placed in 28 of the 30 cases; 15 procedures involved the lower abdomen or pelvis and 13 were confined to a lower extremity. There were three instances in which the catheter could not be advanced into the subarachnoid space following successful dural puncture. However, in one case the flow of CSF was minimal despite the patient being in the sitting position. CSF could be freely aspirated from all but one of the successfully placed catheters, and there were no episodes of intraoperative catheter failure. Lidocaine (either 5% or 2%) was used exclusively. The average (± SD) preoperative dose was 38.9 mg (± 30.7); the range was from 10 to 130 mg. This resulted in an average level of T10 (± 4 segments). The total lidocaine requirement averaged 34.8 mg/hr (± 24.0). These doses were similar to those used with the larger catheter (preoperative dose, 35.8 mg ± 27.9; hourly requirement, 32.4 mg ± 10.2).

All catheters were removed intact. Six of the patients arrived in the recovery room with no detectable motor or sensory block. On the average, patients met the criteria for discharge from the PACU 73 minutes after arrival.

Four patients reported a headache; two of the headaches persisted more than a few hours. One blood patch was performed. The patient that received the blood patch was one of the two patients in whom a subarachnoid catheter was not successfully passed.

Discussion:

Continuous spinal anesthesia is a relatively old technique, having been first described in 1907.[2] A major refinement occurred in 1944, when use of a stiff needle was replaced with a catheter threaded into the subarachnoid space.[3] Recently, Hurley and Lambert reported the use of a 32 gauge polyimide catheter passed through a standard 26 gauge needle.[4] Their initial experience was somewhat unsatisfactory; difficulties in catheter placement and external kinking resulted in a 33% failure rate. These problems were significantly reduced by two modifications in the technique; a threading assist device was added, and the stylet was left in place. However, despite those improvements, catheter breakage remained a serious problem.

The results of the present study demonstrate that a 22 gauge compatible catheter can be used with minimal difficulty. Although injection of local anesthetic is through a single opening at the tip, the catheter performs similarly to an epidural catheter with several proximal holes. Obviously, to decrease the risk of post dural puncture headache it is desirable to utilize the smallest needle possible. Whether difficulties associated with further reduction in catheter size outweigh the benefit needs to be determined.

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TITLE: LACK OF PROLONGED RECOVERY DESPITE POTENTIATED ONSET OF MIXED ATRACURIUM AND VECURONIUM BLOCKADE

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Introduction: We have previously shown the potentiation of neuromuscular blockade when the two intermediate acting muscle relaxants are used in combination.[1] Concern has been raised about the possibility of prolonged blockade when the benzylisoquinolinium and steroidal relaxants are used together. We therefore undertook a study to examine recovery of neuromuscular blockade following the combination of atracurium and vecuronium.

Methods: Thirteen ASA I or II patients, 18 to 65 years old were recruited following Institutional Review Board approved informed consent. They were free from cardiovascular, hepatic, renal or neuromuscular disease and were not on any medications known to effect neuromuscular transmission. Following premedication with diazepam 5-10 mg po and/or midazolam 1-3 mg iv, anesthesia was induced with thiopental 3-5 mg/kg and fentanyl 2-4 mcg/kg iv. Patients were maintained on isoflurane with an end-tidal concentration of 0.8% in 60% nitrous oxide and 40% oxygen. Muscle relaxation was monitored by the integrated EMG of the first interosseous muscle in response to supermaximal train-of-four (TOF) stimulation of the ulnar nerve by surface electrodes at the wrist. Following baseline measurements, a combination of atracurium and vecuronium in dosages previously calculated to yield between 95 and 100% depression of T1 was given. Normothermia (35°-37°C) and normocapnia (end-tidal PCO_2 34-40 mmHg) was maintained. Following spontaneous recovery of T_1 to at least 75% of control, reversal was accomplished with neostigmine and glycopyrrolate.

Results: Patient data and results are shown in Table 1. The average maximum depression of T1 (first twitch of TOF) was 99.1 ± 1.3 %. Maximum response occurred following an average of 169.7 ± 43.3 mcg/kg of atracurium combined with 28.5 ± 7.05 mcg/kg of vecuronium. Time from injection to 25% spontaneous recovery (clinical duration) was 33.3 ± 7.6 minutes, while time for 25 to 75% spontaneous recovery (Recovery Index) was 10.7 ± 2.6 minutes.

Table 1
n = 13
*p<0.01

	Mean ± SD
Age (years)	37.5 ± 11.2
Weight (kg)	72.3 ± 16.1
Atracurium Dose (mcg/kg)	169.7 ± 43.3
Vecuronium Dose (mcg/kg)	28.5 ± 7.05
Time to Maximum Block (min)	6.3 ± 2.6
Clinical Duration (min)	33.3 ± 7.6 *
Recovery Index (min)	10.7 ± 2.6

Discussion: We have demonstrated the lack of prolonged neuromuscular blockade from a mixture of the two classes of intermediate acting relaxants despite achieving a similar degree of blockade. When compared with either atracurium or vecuronium alone under balanced anesthesia, a significantly shorter clinical duration[2] was found with the combination ($p<0.01$) though recovery index[3] was unchanged. This is most likely due to the decreased individual doses necessary for muscle relaxation favoring redistribution kinetics. These findings using the intermediate acting relaxants support those of certain long acting relaxants used in combination.[3,4] The underlying mechanism for the significant potentiation during onset of neuromuscular blockade without prolonged recovery times is currently under investigation.

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TITLE: ONSET, DURATION, RECOVERY AND HEMODYNAMIC EFFECTS OF PIPECURONIUM VS. PANCURONIUM, WITH OR WITHOUT ADMINISTRATION OF SUCCINYLCHOLINE, DURING NARCOTIC ANESTHESIA

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INTRODUCTION: Pipecuronium (PIP) has been found to be similar in structure, onset and duration of action to pancuronium (PAN), with minimal cardiovascular effects.[1] It has also been reported[2] that a PIP ED_{95} dose given over 20 min after an intubating dose of succinylcholine (SCh) had a duration and a recovery similar to those obtained by a comparable PIP dose given alone. The purpose of this study was to compare the onset, duration, recovery and hemodynamic effects of PIP with those of PAN, with or without prior administration of SCh.

METHODS: After IRB approval and informed consent, 48 patients were studied. All patients were either ASA physical status I or II, between age 18 and 60, had no major organ system disease and weighed 50-99 kg. Subjects undergoing surgical procedures of 2 hr duration were randomly assigned to one of four groups: I-PAN (100mcg/kg) alone; II-PIP (80mcg/kg) alone; III-SCh (1mg/kg) + PAN (100mcg/kg); and IV-SCh (1mg/kg) + PIP (80mcg/kg). After premedication (Valium 10mg/70kg or Versed 5mg/70kg), anesthesia was induced with fentanyl (5-10mcg/kg) and thiopental (3-6mg/kg). Maintenance of anesthesia was N_2O/O_2 (66/33), and fentanyl or thiopental as needed. Additional doses of PAN (20mcg/kg) and PIP (15mcg/kg) were also given when required to maintain neuromuscular blockade. Ventilation was controlled to maintain the end-tidal pCO_2 between 35-40 mmHg. Esophageal temperature was maintained between 35°-37° by surface warming. After induction, the isometric force of thumb adduction in response to supramaximal ulnar nerve stimulation was recorded as the "control" value, using a train-of-four (TOF) at 2 Hz supramaximal square wave (0.2 msec duration) every 10 sec via surface electrodes. PAN or PIP alone (group I and II) was given as a single bolus over 5 sec and intubation was attempted after maximum neuromuscular blockade. When SCh preceded PAN or PIP (group III and IV), intubation was accomplished at maximum twitch depression; when T1 (first twitch of TOF) reached 70% recovery from control, PAN or PIP was then given. Time from PAN or PIP injection to maximum T_1 blockade (onset), time from PAN or PIP injection to 25% T_1 spontaneous recovery (duration of action), time from 10 to 25% T_1 (spontaneous recovery) and hemodynamic parameters (BP and pulse), were compared between all groups. Statistical analysis were performed utilizing one-way ANOVA and Student's t-test whenever applicable. Differences were considered statistically significant when the p-value was equal or less than 0.01.

RESULTS AND CONCLUSIONS: There was no significant difference in age or weight. Summary neuromuscular data are given in Table 1. Onset times were the same for PAN and PIP, although significantly shorter when they were preceded by SCh. Intubation times were shorter after SCh than when PAN or PIP were used. Intubation conditions were all good to excellent. Analysis of the clinical durations of PAN/PIP did not show any significant difference between any group and results correspond to reported values. The addition of SCh to PIP shortened the mean duration of the drug but not significantly. Finally, the time for spontaneous recovery of T_1 from 10 to 25% of control was similar in all groups (13 to 19 min mean). When reversal was given (with a minimum T_1 of 25%), all patients had adequate clinical recovery at 10 min. Hemodynamic effects of PAN or PIP injection are summarized on Table 2. The cardiovascular stability of PIP is particularly demonstrated with BP in group IV (SCh + PIP) when PIP is given at a distance from induction (which by itself may create a fall in BP). A significant decrease in heart rate in the same group likely reflects the vagotonic effect of fentanyl. In conclusion, our study confirms that, during a N_2O/O_2 - narcotic anesthesia, PIP has a very similar neuromuscular pharmacological profile to PAN, with no evidence of hemodynamic effects. It also demonstrates that the use of SCh for endotracheal intubation prior to the injection of PIP does not significantly affect the intensity, the time course and the recovery of the drug given alone. This same finding was made with PAN, in agreement with previous reports.[3]

TABLE 1.	I-PAN	II-PIP	III-SCh+PAN	IV-SCh+PIP
ONSET (min)*	2.5 [1.0]	2.8 [0.6]	1.4 [0.4]	1.6 [0.4]
INTUBATION (min)*	2.7 [0.7]	3.3 [0.9]	1.7 [0.5]	1.7 [0.6]
CLIN. DURATION (min)	90 [33]	107 [45]	89 [35]	78 [12]
10-25% RECOVERY(min)	15 [7]	19 [4]	19 [6]	13 [6]

MEAN [STANDARD DEVIATION] * FOR ONSET AND INTUBATION TIMES, GROUPS I & II ARE SIGNIFICANTLY DIFFERENT FROM GROUPS III & IV AT $p \le 0.01$

TABLE 2.	I-PAN		II-PIP		III-SCh+PAN		IV-SCh+PIP	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
SBP	122 [14]	109 [18]	132 [14]	109* [8]	127 [12]	100* [10]	111 [19]	109 [8]
DBP	71 [11]	72 [18]	81 [11]	61* [10]	76 [9]	63* [11]	70 [16]	57 [9]
HR	80 [12]	89 [13]	84 [13]	77 [12]	92 [24]	85 [18]	81 [16]	69* [14]

VALUES ARE MEAN [STANDARD DEVIATION] HR = HEART RATE SBP = SYSTOLIC BLOOD PRESSURE DBP = DIASTOLIC BLOOD PRESSURE * POST-INJECTION VALUE SIGNIFICANTLY DIFFERS FROM PRE-INJECTION AT $p < 0.01$

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Title: Long term follow up for identification of anesthetic complications

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Introduction. Studies of anesthetic complications vary widely in the post-operative follow up period during which anesthetic complications are identified.[1,2] To date, no studies have demonstrated that long term follow up of patients can identify additional anesthetic complications not identified in the first 48 hours post-operatively.

As a part of a quality assurance program begun in 1988, post-operative questionnaires were sent to patients at home to identify areas of dissatisfaction. This report presents data obtained during the initial 7 months of this program that bears on complications not identified during routine follow up.

Methods. Beginning in February, 1988 all patients receiving anesthesia were mailed a standardized questionnaire inquiring about patient satisfaction with their anesthetic care. The questionnaires were mailed to patients 4 to 6 weeks post-operatively. Specifically, the questionnaire asked whether the patient had experienced problems attributable to anesthesia. One questionnaire was sent for each anesthetic performed, therefore, multiple questionnaires were sent to some patients. Patients were excluded if they had received anesthesia for OB procedures (OB anesthesia has its own QA program) or ECT, if they had received only monitored anesthetic care, if they resided in a chronic care facility or prison, or if they were deceased.

All questionnaires returned which indicated an anesthetic problem were reviewed by a single certified registered nurse anesthetist. Review included in depth chart review, a telephone interview with the patient and arrangements for follow up care, if indicated.

Results. To date 7051 questionnaires have been sent. Thus far, 4056 questionnaires have been returned (57% return rate). In 7 cases injuries likely due to anesthesia were documented that had not been identified by the anesthesia service during the patient's hospitalization. In one case, the patient complained of difficulty swallowing secondary to a laceration of the pharynx. The patient was seen repeatedly in the otolaryngology clinic but the anesthesia department had not been notified. One patient suffered a lip laceration, apparently during intubation. In this case no post anesthetic visit was documented and the nursing notes failed to mention the complication. In one case tooth damage was noted by the patient only after discharge. There were 2 cases wherein post spinal headaches developed after discharge. Both patients had received a spinal anesthetic for a nephrolithotripsy. One headache resolved spontaneously after 3 days, while the other case required a blood patch at a local hospital. Two cases of post-operative nerve palsies were identified. In one case paresthesias in the distribution of the ulnar nerve were identified in a patient following thoracotomy. The injury was not identified during the hospitalization because the patient did not consider it significant. The paresthesia has continued for more than 4 months with little resolution. In the other case persistent paresthesias in the ulnar nerve distribution were identified in a patient following total hip replacement. The paresthesia was noted after the post anesthetic visit had been performed. Follow up was arranged for this patient.

Discussion. This series has demonstrated that routine post anesthetic notes obtained <48 hours post-operatively will fail to identify some patients who experience complications related to anesthesia. Further, studies of anesthetic risk that limit the follow up period to <48 hours may underestimate the true incidence of anesthetic morbidity. In our series more than 1 per 1000 patients experienced complications not identified until >48 hours post-operatively. Previously Cohen et al. reported that nerve palsy occurred at a rate of 1.6 per 10,000 and that dental damage occurred at a rate of 9.9 per 10,000.[3] If our data is combined with the short term follow up of Cohen, nerve palsy would be noted to occur at a rate of 4.4 per 10,000 and dental damage would occur at a rate of 11.3 per 10,000. Thus, this data suggests that anesthetic complications may occur at a rate higher than previously expected. This data also suggests a need for systematic long term follow up of patients following anesthesia.

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Title: PLACENTAL TRANSFER OF ISOFLURANE AND HALOTHANE DURING CESAREAN SECTION

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Introduction

The ideal anesthetic agent for obstetrics would prevent awareness in the mother, while having minimal depressant effect on the fetus. Isoflurane has recently been reported as a suitable anaesthetic agent for Cesarean Section.[1] We set out to compare the placental transfer of isoflurane and halothane during Cesarean Section.

Methods

Twenty patients presenting for elective Cesarean Section were studied. Informed consent was obtained from all patients and approval had been granted by the University Research Ethical Committee. All were healthy, and patients with pre-eclampsia or placental insufficiency were excluded. Patients were randomly allocated to receive halothane or isoflurane as part of their anesthetic.

After induction of anesthesia with thiopentone and succinyl choline, the trachea was intubated and ventilation was continued with 50% N_2O in O_2. A non-depolarising muscle relaxant was administered to facilitate surgery. The volatile anesthetic agent was added to the inspiratory gas in a concentration of 0.8% for isoflurane or 0.5% for halothane. Venilation was adjusted to maintain the end-tidal CO_2 tension at 32 torr. A 22g cannula was inserted into the radial artery for blood sampling.

Samples of maternal arterial blood were drawn at 5 and 10 minutes after the introduction of the volatile agent and at delivery of the fetus. Fetal blood samples were drawn from the umbilical vein and artery immediately after delivery. A sample of the inspired gas was taken for estimation of the inspired partial pressure of volatile agent. Samples were drawn into glass, gas tight syringes and sealed with a Teflon stopcock until analysis. The partial pressure of the volatile agent in blood was calculated using the equilibration method described by Fink (1970)[2]. Maternal arterial and fetal umbilical venous samples were taken at delivery for blood gas analysis.

Results

Eleven patients received halothane and 9 received isoflurane. Patients receiving halothane and isoflurane were of similar age, gestation and parity. Mean induction - delivery time was similar in both groups (10.8 min for halothane, 12.1 for isoflurane). Mean fetal and maternal pH were similar in the groups receiving halothane and isoflurane. Apgar scores at 1 and 5 min after delivery were similar in both groups.

Mean ratios (SD) of maternal blood to inspired partial pressure of the volatile agent at delivery were 0.351(0.061) for halothane and 0.431 (0.081) for isoflurane. Mean ratios (SD) of umbilical vein to maternal arterial partial pressures of volatile agent at delivery was 0.712 (0.148) for halothane and 0.717 (0.085) for isoflurane. Mean ratio (SD) of umbilical vein to umbilical artery partial pressure was 2.92 (1.07) for halothane and 2.61 (0.92) for isoflurane.

Discussion

The placental transfer of isoflurane is similar to that of halothane and fetal isoflurane tensions depend largely on maternal arterial tensions. As maternal arterial tensions of isoflurane rise more rapidly than those of halothane, so too will fetal tensions. This had no adverse effect on fetal wellbeing.

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Title: PROPRANOLOL IS EFFECTIVE FOR PREOPERATIVE ANXIOLYSIS IN OUTPATIENTS

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Introduction: Beta blockers effectively prevent stage fright,[1] and therefore they may be useful as nonsedating anxiolytic agents prior to outpatient surgery. The utility of propranolol for anxiolysis prior to surgery has not previously been studied. We undertook this study to compare the effects of propranolol, diazepam, and placebo, for anxiolysis prior to outpatient surgery and to compare the effect of these agents on post operative recovery of cognitive function.

Methods: The study was approved by the Hospital Ethics Committee and consent was obtained from 92 healthy ASA I females aged 15-42 years undergoing outpatient therapeutic dilatation and curretage (D&C). In randomized double blind fashion the patients received one of the following oral medications 1-1.5 hr preoperatively: 1) diazepam 10 mg (n=31), 2) propranolol 80 mg (n=31), 3) placebo (n=30)

Assessments of anxiety using the State Trait Anxiety Inventory [2] (STAI) were performed on arrival at the hospital, in the holding area outside the OR (1 hour after the premedication) and 2 hrs post operatively. Post operative recovery was assessed using the Trieger Test and Digit Span on admission to hospital and at 1, 2, and 3 hours after the operation. The anesthetic was standardized to include fentanyl 0.5 μg/kg, pentothal 5mg/kg with an additional 1 mg/kg prior to dilatation of the cervix. Maintenance was with 60% N_2O, and enflurane titrated to signs of light anesthesia. Statistical analysis was performed using repeated measures analysis of variance within groups and analysis of variance with Bonferroni correction between groups, accepting $p < 0.05$ as significant. The anxiety data was considered nonparametric and analyzed with the Kruskal-Wallis test and the signed rank test.

Results: There were no significant differences between the groups with respect to age, weight, duration of the operation, or baseline scores on the State Trait Anxiety, Trieger, or Digit Span tests. Between group comparison of anxiety showed no significant difference among patients receiving propranolol, diazepam, or placebo (Fig 1). All medication groups showed a significant decrease in anxiety between admission to hospital and both subsequent assessments of anxiety after administration of the premedication (Fig 1).

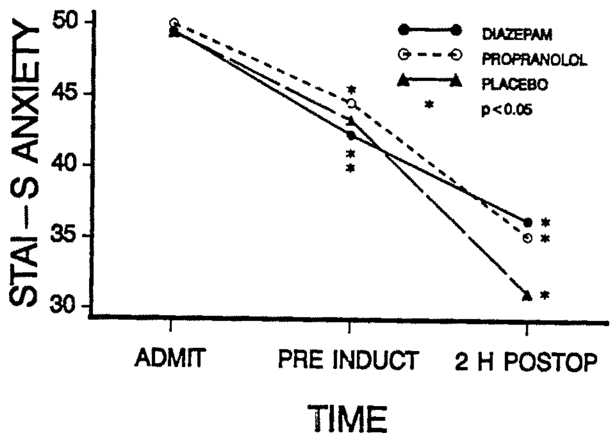

Fig. 1 - Anxiety vs Time

Trieger testing showed a decrement in performance in all three groups at 1 hour. This resolved by 2 hours in those patients given propranolol but required 3 hours for resolution when either diazepam or placebo tablets were administered. Performance on the Digit Span test was only decreased at 1 hour post operatively in the diazepam and placebo groups.

Discussion: Propranolol, diazepam, and placebo were all effective in the treatment of preoperative anxiety for outpatient suction D&C. No difference in anxiolytic properties could be demonstrated among the three premedications. Return to baseline psychomotor status was fastest in the patients receiving propranolol.

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Title: ALFENTANIL AND NITROUS OXIDE PRODUCE ADEQUATE AMNESIA

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Introduction: Awareness during anesthesia is distressing for patients expecting total amnesia during their general anesthetic. State of the art anesthetic monitoring equipment is not capable of consistently differentiating patients who are aware of their surroundings from patients who are not. In this study we anaesthetized our patients with a narcotic/nitrous oxide/muscle relaxant technique. Postoperatively we tested the patients for subconscious memory of the intraoperative period.

Methods: After approval from the Clinical Trials Committee, consent was obtained from 38 patients (34 ± 12 years) scheduled to have a general anesthetic of approximately 1 hour duration. Patients were excluded from study if they had a hearing deficit, less then grade 9 education, chronically using psychotropic medications, did not speak English as a native language, or the anesthetist in charge of the case felt that the patient was not suitable for the standardized anesthetic. No premedication was administered. The anesthetic was standardized to include defasiculation with pancuronium 20 μg/kg followed by pentothal 2 mg/kg, alfentanil 85 μg/kg, and succinylcholine 1.5 mg/kg. Post induction hypotension, if present, was treated with norepinephrine as a single bolus of 0.1 μg/kg and partial paralysis was titrated with vecuronium. Anesthesia was maintained with nitrous oxide end tidal concentration 66% and alfentanil boluses of 7-14 μg/kg when any of the following signs of light anesthesia were observed:

1) Increase in systolic BP 15 mm Hg above baseline
2) HR > 90 bpm in the absence of hypovolemia
3) Movement
4) Autonomic signs such as lacrimation, sweating, flushing

Patients were ventilated to an end tidal CO_2 of 35-40 torr. Reversal of neuromuscular blockade was accomplished with neostigmine 2.5 mg and glycopyrrolate.0.4 mg.

Throughout the entire maintenance phase of anesthesia, patients were presented with auditory stimuli at comfortable listening volume through occlusive headphones. The stimuli consisted of 20 homophone phrases and 20 single words.

- Homophone Test

Homophones are words which are identical in pronunciation, but different in both spelling and meaning such as ATE and EIGHT. The homophone test requires subjects, given no context, to spell a list of 20 homophones and 10 non-homophone distractor words. The proportion of the 20 homophones spelled according to the most common interpretation can be compared with and without pretest biasing. Bias stimuli consists of phrases using the homophone in its least common context e.g. "An octopus has EIGHT legs."[1]

One hundred subjects were unbiased before testing, 38 subjects heard the bias stimuli only during the maintenance phase of anesthesia, and 26 subjects were biased while awake. ANOVA with post hoc Scheffe's test was used to compare the proportion of homophones chosen according to the most common interpretation between the three groups.

- Familiar Word Test

Two lists of 20 low frequency words were selected from Battig and Montague category norms[2] on the basis of infrequent use in the English language. In counterbalanced fashion, patients were presented with either list A or B. Post presentation testing required the patient to make a forced choice between two words of which only one had previously been presented. Results were interpreted using the students t test against a score of 10/20 which would be rendered through chance alone. Thirty eight subjects heard the word list during the maintenance phase of anesthesia, and 26 subjects heard the word list while awake.

All testing was carried out between 2-3 hours after the initial presentation of the homophone or familiar word stimuli.

Results: The average anesthetic duration was 1.08 hours and total Alfentanil dose was 9611 mic (112 mic/kg/hr). The Homophone test (Table 1) and the Familiar Word test (Table 2) showed significant bias only in the patients who were awake during the bias presentation. No patients (asleep biased) reported any frank recall of intraoperative events, and the tests of memory could not demonstrate any subconscious recall.

Table 1. Homophone Test

	Sample Size	Homophone Proportion	
Unbiased	100	0.72	Not Signif.
Biased During Anesthesia	38	0.67	Not Signif.
Biased Awake	26	0.49	$p < 0.001$

Table 2. Familiar Word Test

	Sample Size	Familiar Word Score	
Chance Alone	--	10/20	--
Biased During Anesthesia	38	10.34/20	Not Signif.
Biased Awake	26	18.85/20	$p < 0.001$

Discussion: General anesthesia with nitrous oxide 66% and alfentanil titrated to signs of light anesthesia provides adequate amnesia for surgery without any benzodiazepines or halogenated volatile anesthetics.

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Title: TRENDELENBURG POSITION VS. PASSIVE LEG RAISING: HEMODYNAMIC EFFECTS AND VOLUME SHIFTS

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Introduction: Both the Trendelenburg position (T) and passive leg raising (R) are clinically employed in order to increase blood pressure and cardiac output in a quick, non-invasive and reversible manner. Nevertheless, the relative effectiveness of these maneuvers and their mechanisms of action are still controversial (1,2,3). We studied the contribution of intravascular volume shifts and systemic vascular resistance (SVR) changes to hemodynamic effects of T and R in awake and anaesthetized patients.

Methods: After obtaining institutional approval and written informed consent, we assigned 29 patients undergoing coronary artery bypass grafting randomly either to group T (n=15) or R (n=14). Radial and pulmonary arterial catheterizations were performed under local anaesthesia and sedation (i.v. flunitrazepam 0.01 mg/kg). Anaesthesia was induced using fentanyl (i.v. 20 ug/kg) and etomidate (i.v. 0.1 mg/kg). After tracheal intubation, controlled ventilation was maintained with an $FiO_2=1.0$, and a catheter was placed into the inferior vena cava (IVC) via a femoral vein. Hypothermic (28 C) cardiopulmonary bypass (CPB) was performed with cannulation and ligature of both venae cavae, diverting the entire venous return to the reservoir. Hemodynamic measurements during spontaneous circulation included heart rate (HR), systolic and diastolic arterial, right atrial (RA), pulmonary arterial (PAP) and wedge pressures (PC) as well as thermodilution cardiac outputs. During CPB with the aorta cross-clamped, pump flow (PF), mean arterial (MAP) and IVC pressures and the reservoir volume (RV) of the CPB circuit were recorded. Cardiac index (CI), stroke index (SI) and SVR index (SVRI) were calculated. Hemodynamic measurements were obtained in each patient while awake, anaesthetized and during CPB with a fixed PF of 2.3-2.4 l/min*m2. Under the first two conditions 4 sets of measurements were made: Control, 3 and 8 min after changing to either a 15 head down tilt (group T) or to leg raising to 45 (group R), and again in the horizontal supine position. During CPB, parameters were monitored prior to and 3 min after positioning only, in order not to interfere with declamping of the aorta. Statistical analysis was performed using Fisher's Exact Test, Wilcoxon's test and ANOVA for repeated measurements. Values are given as mean ±SEM. $p<0.05$ was regarded as significant.

Table 1.

Group T	awake	anaesthesia	CPB
PC supine	4.7±0.5	4.3±0.4	---
3 min T	6.6±0.8	6.4±0.6	---
CI supine	2.40±0.10	2.30±0.10	2.28±0.04
3 min T	2.67±0.11	2.65±0.09	2.28±0.04
MAP supine	83.7±2.3	74.6±2.3	73.9±1.7
3 min T	82.3±2.4	80.0±2.5	75.1±2.4

Results: Groups R and T did not differ with patients in horizontal position. With position change, in both groups T (Table 1) and R (Table 2), whether awake or anaesthetized, HR and SVRI decreased, and PAP, RA, PC, CI and SI increased compared to control ($P<0.001$), with a greater increase of CI in group R while awake ($p<0.05$).
CI and SI remained elevated for 8 min under all conditions. In group R, whether awake or anesthetized, MAP rose and was maintained for 8 min ($p<0.001$). In group T, awake, MAP did not change at all, whereas under anesthesia MAP increased initially, but returned to control levels within the following 5 min.
During CPB, T increased RV by 343±68 ml, whereas R increased RV by 273±53 ml (NS). SVRI was slightly elevated after both maneuvers on CPB (R/T vs. supine: $p<0.025$; R vs. T: NS).

Discussion: These data demonstrate that in patients with mild hypovolemia R and T are both effective in increasing CI for 8 min. Baroreceptor reflex activity may play a greater role during T than R, because MAP remained constant while the increase in CI was less marked in T. In awake patients, R may be clinically superior to T, if a maximal increase in MAP and CI is desired. CPB with fixed PF and free venous drainage allowed us to quantify venous return and SVRI due to position changes without cardiac effects. Based on an estimation of total blood volume (EBV), there was a volume shift of 5-7 % of EBV to the intrathoracic venae cavae, which is probably the principal mechanism for the increases in CI. This value is higher than that reported for T in normovolemic awake subjects using radiolabelled red cell scanning (3). Though also seen with CPB, small increases in SVRI are overcome by reflex mechanisms during spontaneous circulation.

References:
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Table 2. (Mean±SEM; PC,MAP: mmHg; CI: l/min*m2)

Group R	awake	anaesthesia	CPB
PC supine	4.9±0.5	5.1±0.5	---
3 min R	6.6±0.5	7.3±0.6	---
CI supine	2.35±0.13	2.03±0.13	2.40±0.04
3 min R	2.76±0.15	2.37±0.14	2.41±0.04
MAP supine	87.5±3.0	71.2±2.5	74.1±5.0
3 min R	93.3±2.8	80.5±2.7	80.2±5.2

Title: MIDAZOLAM & FENTANYL EFFECTS ON MUSCLE SYMPATHETIC NERVE ACTIVITY & BAROREFLEX FUNCTION IN HUMANS

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Introduction

Fentanyl (F) and midazolam (M) are often administered for anxiolysis and sedation in the preoperative setting. On occasion, relatively small IV doses of these agents have produced unexpected hypotension. The mechanism of this response is uncertain. To determine the effect of F and M on blood pressure regulating mechanisms, we employed percutaneous recordings of efferent sympathetic nerve activity directed to blood vessels supplying skeletal muscle (MSNA) during administration of sedative doses of midazolam (1 mg), fentanyl (100 ug) or placebo (P) to volunteers. In addition, augmentations in MSNA and HR were provoked by brief reductions in BP (sodium nitroprusside: SNP) to determine the effects of F and M on baroreflex function.

Methods

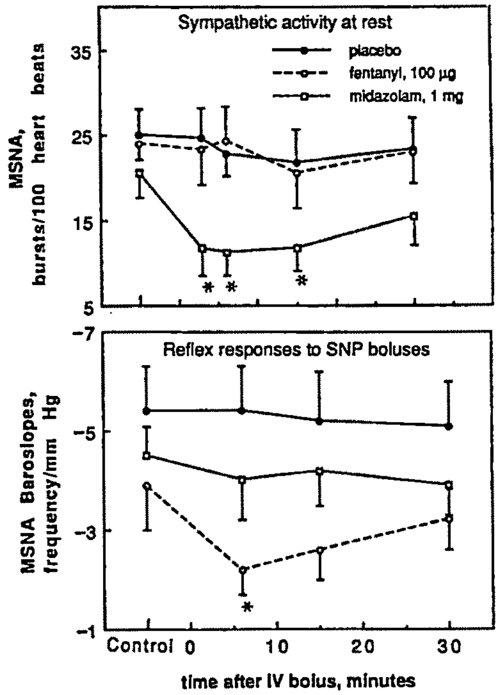
This study was approved by the institutions' research review committees and written, informed consent was obtained from each of 18 volunteers. Monitoring consisted of lead II ECG, a radial artery catheter and a bellows on the abdomen to record respiration. A 5-micron tipped, epoxy-coated tungsten needle was inserted below the head of the fibula and advanced into a nerve fascicle within the peroneal nerve that innervated muscle (confirmed by electrical stimuli). The signal was amplified 100,000x, integrated and displayed. Recordings from sympathetic nerves were sought by small manipulations of the needle within the fascicle until characteristic sympathetic bursts were obtained. A 10-min control period was observed, followed by a 3-min period of hypotension produced by a 100 ug bolus of SNP. After a 10-min recovery, 7 subjects received IV M, 5 subjects received IV F and 6 subjects received P, and data were collected for an additional 33 min. SNP boluses were repeated at min 7, 20 and 30 after drug administration. Results were compared with repeated measures ANOVA.

Results

There were no differences between groups in each of the measured variables at baseline. Administration of F, M or P did not alter respiratory rate or HR. Both F and M elicited significant ($p<0.05$) reductions in MAP (F = $-5.9 \pm 2.5\%$, M = $-4.1 \pm 1.6\%$, respectively; mean ± SEM). These decreases occurred within 2 min of IV injection of F or M, lasted about 10 min and were not associated with reflex tachycardia. Only M reduced MSNA (figure). Baroreflex slopes relating reductions in SBP to R-R interval responses were similar in all groups at baseline and unchanged by F, M or P administration. However, baroreflex increases in MSNA were blunted by F but unchanged by M and P (figure).

Discussion

Administration of sedative doses of fentanyl and midazolam produced a transient decrease in BP. In subjects receiving midazolam, this response could be attributed to reductions in sympathetic outflow to blood vessels supplying skeletal muscle. The reduction in BP in the group receiving fentanyl was not due to decreased MSNA which suggests this hypotension was due to changes in sympathetic activity to other vascular beds or due to direct effects on vascular smooth muscle. The fentanyl and midazolam induced decrease in BP without a reflex increase in HR and the demonstration of unchanged R-R interval baroreflex slopes indicate that fentanyl and midazolam reset the heart rate limb of the baroreflex to a lower operating point. Midazolam also appears to lower the operating point without altering the gain of the baroreflex control of MSNA. However, in contrast to midazolam, fentanyl decreased the gain (slope) of the baroreflex control of MSNA.



* Significant difference from other groups ($p<0.05$)

TITLE: DO LV MASS AND LV FUNCTION, AS MEASURED BY TEE, PREDICT POSTOPERATIVE OUTCOME AFTER NON-CARDIAC SURGERY?

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INTRODUCTION

Left ventricular hypertrophy (LVH) is common in patients (pts) with chronic hypertension (HTN). HTN is common in patients undergoing vascular surgery. The presence of LVH has been shown to increase morbidity and mortality in pts with hypertension followed chronically.[1]

Pts with decreased ejection fraction (EF) have been shown to have increased long-term mortality after vascular surgery, but perioperative rates of myocardial infarction and death are not different from patients with normal ventricular function.[2]

We hypothesized that pts with LVH would have a greater rate of perioperative cardiac morbidity. We also hypothesized that pts with an ejection fraction of < 40% would not have an increased rate of congestive heart failure (CHF).

METHODS

34 pts were studied during non-cardiac surgery, predominantly vascular procedures. Pts had two or more of the following risk factors: (i) age > 70 years, (ii) known coronary artery disease, (iii) peripheral vascular disease, (iv) HTN, (v) chronic renal failure. Pts gave informed oral consent for data collection as approved by our Institutional Review Board.

Anesthesia was induced and maintained with isoflurane, sufentanil, oxygen, and a non-depolarizing relaxant. The use of invasive pressure monitoring was not dictated by the study.

After intubation, a transesophageal echocardiographic (TEE) probe was placed and long-axis and short axis, mid-papillary views were obtained. The videotapes were analyzed afterwards to measure the length of the LV cavity from the mitral annulus to the endocardial border (L_{endo}) and to the epicardial border (L_{epi}). In the short axis view, the end-systolic area (A_{sys}) was measured. End-diastolic areas of the LV were measured for the cavity (A_{cav}) and the muscle plus cavity (A_{musc}). LV mass, normalized for BSA was calculated as $1.055\ (5/6)[(A_{musc})(L_{epi}) - (A_{cav})(L_{endo})]/BSA$.[3]

Area ejection fraction ($EF_a = 100*(A_{cav} - A_{sys})/A_{cav}$) was measured from the short axis view.

Pts were visited on postoperative days 1 and 3. The presence of CHF was established when at least two of the following existed: (i) rales on physical examination by the housestaff, (ii) the use of IV therapy to treat fluid overload, (iii) a chest radiograph read by radiologists as consistent with pulmonary congestion, and (iv) a PCWP > 15 mmHg.

RESULTS

Of 34 patients with analysis of LV mass, 14 were diagnosed as having post-operative congestive failure. 7 of 22 patients with LV mass < 120 g/m^2 had CHF; 7 of 12 patients with LV mass > 120 g/m^2 had CHF ($0.2 < p < 0.3$ by Chi-squared analysis); see table 1.

36 patients had EF measurements; 4 of 10 pts with EF < 40% had CHF, whereas 11 of 26 patients with EF > 40% had CHF ($0.8 < P < 0.9$) by Chi-squared analysis); see table 2.

DISCUSSION:

Low EF did not predict post-operative congestion in high risk patients after noncardiac surgery. Our data agrees with that of Kazmers et al[2], who found no increased perioperative morbidity in patients with low EF (though long term morbidity was increased). Careful anesthetic management may account for this lack of correlation between EF and postoperative CHF. It is also possible that the existence of areas of myocardium with the potential for reversible ischemia is what places patients at greater risk; dipyridamole thallium scanning can detect such areas.[4] Dynamic testing may be necessary for risk stratification, as baseline EF does not seem predictive.

Pts with LVH may be predisposed to CHF in the perioperative period due to diminished diastolic compliance and poor subendocardial perfusion. Our data for LV mass approaches significance; analysis of a larger cohort may reveal statistical significance.

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TABLE 1

	LV mass < 120	>120 g/m^2
postop chf	7	7
no postop chf	15	5

$0.2 < P < 0.3$

TABLE 2

	EF > 40%	EF < 40%
postop chf	11	4
no postop chf	15	6

$0.8 < P < 0.9$

Title: Incendiary Potential of the Flashlamp-Pumped 585nm Pulsed Tunable Dye Laser

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__Introduction.__ The pulsed flash-lamp pumped tunable dye laser is the treatment modality of choice for port-wine stains, congenital cutaneous lesions most often found on the face.[1] While most adults and adolescents usually tolerate the stinging pain caused by this device, infants and younger children usually require anesthesia. While some have reported success with topical anesthetic creams, we have not had good results with this approach and have been inducing general anesthesia by mask or providing intravenous sedation.

The laser generates a 585nm pulse which is selectively absorbed by oxyhemoglobin and causes photothermolysis of the abnormal blood vessels that cause the port-wine stain. Because of the selective nature of absorption and the brief (450 μsec) duration of the pulse, non-specific heat diffusion and adjacent tissue damage is minimized. Since we are using supplemental oxygen during these cases, we designed this study to determine the laser's potential to causea fire in the presence of oxygen and nitrous oxide. The port-wine stains often extend into the eyebrows and the hair line, and the eyes are often protected with gauze, so we used gauze test strips and human hair as the ignition test materials.

__Methods.__ A flashlamp-pumped 585nm pulsed tunable dye laser (Candela Laser, Corporation, Wayland, MA) with a 5mm diameter spot size was used. Energy output was calibrated with a laser power energy meter (Ophir Optics, LTD, Jerusalem, Israel). 1 cm^2 single ply thickness gauze (Johnson and Johnson, New Brunswick, NJ), 1 cm^2 Telfa pads (The Kendall Company, Boston, MA), and dark brown human hair (from RHE) were used as the test materials. The test patches were used dry or saturated with saline or isopropyl alcohol. Oxygen and nitrous oxide were administered from an Ohio 30/70 Proportioner anesthesia machine, and gas concentrations measured using a Puritan-Bennett Datex 254 Airway Gas Monitor. Energy output from the laser ranged between 6.0 and 10.0 Joules/cm^2, within the clinical dose range.

__Results.__ We were unable to ignite the gauze or Telfa in room air using the highest tested energy level, even when these materials were soaked in isopropyl alcohol. (Table 1) In the presence of 100% oxygen directed at the test patch, the gauze ignited at 9.0 J/cm^2 but failed to ignite despite 20 pulses between 8.0 and 8.5 J/cm^2; we were unable to ignite the Telfa test patches with 10.0 J/cm_2 in the presence of 100% O_2. Ignition of gauze at 10 J/cm^2 in the presence of 100% O^2 could be prevented by soaking the gauze with saline. With a 70% nitrous oxide 30% oxygen mixture directed at the gauze test patch, we were unable to cause ignition at 10 J/cm^2.

When hair was used as the test material, it flamed in room air at energy levels as low as 6.0 J/cm^2, and sporadically ignited at energy levels greater than or equal to 8.0 J/cm^2. (Table 2) When the hair was soaked in saline, the flame generated by the laser in room air was considerably smaller and it did not ignite at 10.0 J/cm^2. In the presence of 100% O_2, 70% N_2O/30% O_2, or 100% O_2 and saline, the hair ignited at 6.0 J/cm^2.

__Discussion.__ Because of the potential for causing a fire, one should not direct supplemental oxygen into the laser field. Since the lesions are usually on the face, this requires a tight mask fit and removing the mask from the face when lesions around the mouth, nose, and eyes need to be treated. Gauze or Telfa pads used to protect the eyes should be soaked in saline and care taken not to hit them with the laser beam. We found hair to be particularly flammable, even at the lowest clinically useful laser energy output level, and extreme care must be taken not to direct O_2 or N_2O into the laser field when this is adjacent to eyebrows or the scalp. While soaking the hair in saline minimizes the risk of ignition in room air, this protection is eliminated in the presence of supplemental O_2. Cleaning the skin with inflammatory substances prior to the laser treatment should be avoided, as should the use of hair products with similar potential.

Table 1. Ignition of Gauze Patches by the Flashlamp-pumped 585nm Tunable Dye Laser

__Patches Ignited/Test Firings__

Laser E J/cm^2	Test Matl	RA	ALC + RA	O_2	ALC + O_2	SAL + O_2	N_2O + O_2
6.0	gauze	0/3	0/3	0/3	0/3	0/3	0/3
7.0	gauze	0/3	0/3	0/3	0/3	0/3	0/3
8.0	gauze	0/3	0/3	0/10	0/3	0/3	0/3
8.5	gauze	-	-	0/10	-	-	-
9.0	gauze	0/3	0/3	1/5	1/9	0/3	0/3
10.0	gauze	0/10	0/10	2/5	1/7	0/10	0/10
8.0	Telfa	-	-	-	0/10	-	-
9.0	Telfa	-	-	-	0/10	-	-
10.0	Telfa	0/10	0/10	0/10	1/3	-	-

RA=room air ALC=isopropyl alcohol SAL=saline
- =not determined O_2=oxygen N_2O=nitrous oxide

Table 2. Ignition of Hair by the Flashlamp-pumped 585nm Tunable Dye Laser

__Flamed/Ignited/Test Firings__

Laser E J/cm^2	Test Matl	RA	SAL + RA	O_2	SAL + O_2	N_2O + O_2
6.0	hair	10/0/10	3/0/3	2/1/2	2/1/2	5/1/5
7.0	hair	10/0/10	3/0/3	-	-	-
8.0	hair	9/1/9	3/0/3	-	-	-
9.0	hair	7/1/7	20/0/20	-	-	-
10.0	hair	8/1/8	-	-	-	-

__References.__
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TITLE: VENTILATION-PERFUSION ($\dot{V}_A/\dot{Q}$) RELATIONSHIP IN PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY

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Introduction. Cardiopulmonary derangements during total hip arthroplasty (THA) are well recognized. Intraoperative hypotension, hypoxemia, cardiac irregularities, and cardiac arrest are thought to result from increases in intramedullary pressure during the insertion of methylmethacrylate cement and/or prosthesis into the femoral canal with consequent pulmonary embolization of marrow, fat, and/or air. In dogs, there is a greater degree of fat embolism and cardiopulmonary dysfunction with cemented THA (CTHA) than with non-cemented THA (NCTHA).[1] In this study, we used the multiple inert gas elimination technique (MIGET) to compare the $\dot{V}_A/\dot{Q}$ relationship in patients undergoing CTHA or NCTHA.

Methods. With the approval of the Institutional Review Board, 12 patients scheduled for elective total hip arthroplasty (6 CTHA, 6 NCTHA) were studied. Each patient received a standardized total intravenous anesthetic and was monitored with continuous transesophageal echocardiography for evidence of right heart embolization. Patients were studied in the left or right lateral decubitus position. MIGET was used to determine distribution of $\dot{V}_A/\dot{Q}$.[2] Control values were obtained 20 min after turning the patient to the lateral decubitus position. Post-THA measurements were obtained after insertion of the femoral prosthesis. The results are reported as the mean ± SD. T tests were used to compare changes within each group (paired) and to make a comparison between the CTHA and NCTHA groups (unpaired). Significance is defined as $p < 0.05$.

Results. The results are summarized in the table. Statistically significant differences are indicated where appropriate.

Discussion. In a dog model, CTHA was associated with a significantly greater degree of pulmonary embolization and cardiopulmonary dysfunction than a comparable NCTHA group.[2] We commonly observed echocardiographic evidence of right heart embolization in patients undergoing THA and therefore anticipated that lung regions with a high $\dot{V}_A/\dot{Q}$ would develop. Surprisingly, no significant change in the vast majority of parameters measuring cardiovascular function or gas exchange occurred in either group. It is possible that transient changes went undetected because the MIGET is insensitive to fleeting shifts in gas exchange. These findings are also consistent with the observation that fat emboli during THA are usually smaller than 80 μm,[3] i.e., they do not obstruct blood vessels of functional gas exchange units which are subtended by vessels larger than 150 μm.[4] Still unexplained, however, is how echocardiographically visible emboli, occasionally 1-2 cm in diameter, fail to produce significant aberrations in gas exchange.

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Cardiopulmonary Variables (Mean ± SD), $FIO_2 = 1.0$

	Cemented		Non-cemented	
	Control	Post-THA	Control	Post-THA
Age, yrs	72±8		61±6*	
Wt, kg	78±14		75±13	
Ht, cm	166±7		169±8	
VT, ml	906±403	846±271	1008±244	940±220
f, min^{-1}	9±3	10±3	9±2	8±1
PaO_2, mmHg	399±96	422±73	476±39	445±71
$A\text{-}aDO_2$, mmHg	147±64	170±59	119±83	123±83
$PaCO_2$, mmHg	28±5	26±2	27±3	29±3
$a\text{-}ETDCO_2$, mmHg	4±3	6±5	5±2	9±3
Hgb, $g \cdot dl^{-1}$	11.1±1.1	9.4±1.0†	11.1±1.4	9.0±2.4†
Blood Flow				
$\dot{Q}s/\dot{Q}t$, %	8±3	8±3	7±5	9±5
$0<\dot{V}_A/\dot{Q}<0.1$	4.1±3.6	5.2±5.6	9.7±6.9	7.3±8.2
ln SD	1.1±0.3	1.1±0.5	1.3±0.3	1.2±0.4
Ventilation				
V_D/V_T, %	33±12	38±5	28±4	33±7
$10<\dot{V}_A/\dot{Q}<100$	0.0±0.0	0.0±0.0	4.9±7.6	3.7±6.6
ln SD	0.5±0.2	0.3±0.1†	0.8±0.4	0.8±0.4§
Hemodynamics				
$\dot{Q}$, $l \cdot min^{-1}$	3.3±0.6	3.2±0.8	5.3±2.7	4.6±0.9§
HR, min^{-1}	59±8	64±11	61±14	63±11
MAP, mmHg	99±10	95±16	88±13	89±12
MPAP, mmHg	20±5	24±5	18±8	16±4§
PCWP, mmHg	15±3	13±3	11±3	10±2
RAP, mmHg	12±5	10±4	11±3	9±3†

*$p < 0.05$ (unpaired T: CTHA vs. NCTHA)
†$p < 0.05$ (paired T: control vs. post-THA)
§$p < 0.05$ (unpaired T: CTHA vs. NCTHA at control or post-THA)

Title: THE EFFECT OF TRAIN-OF-FOUR ON BLOOD FLOW AND PHARMACODYNAMICS OF VECURONIUM LOADING DOSES IN THE DOG DIAPHRAGM

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Introduction.

Muscle contraction is accompanied by an increase in blood flow.[1] This increase in muscle activity has been shown to affect onset but not recovery time of gallamine, a nondepolarizing muscle relaxant (NDMR), in a perfused dog plantaris-gastrocnemius preparation.[2] Train-of-four (TOF) has been shown to reduce onset times of neuromuscular relaxants in human adductor pollicis.[3] This reduction in onset time had been assumed to be related to an increase in blood flow. More recently it was shown that TOF stimulation increased diaphragmatic blood flow and reduced succinylcholine onset time.[4] Since succinylcholine is a depolarizing muscle relaxant with a short onset time, the relationship between TOF and muscle blood flow changes were evaluated using vecuronium, a NMDR with a longer onset time.

Methods.

Thirteen mongrel dogs (20-40 kg) were studied (with approval of our institutional animal care committee). Anesthesia was induced with pentothal (10 mg/kg), and then maintained with halothane (1%). All animals were supine, intubated and mechanically ventilated to maintain a PO_2 60 mmHg and a $PaCO_2$ between 35-40 mmHg. TOF stimulation of the diaphragm was achieved by a transvenous pacing catheter[5] connected to a Grass S48 stimulator using supramaximal voltages. The evoked response of the diaphragm was measured using transdiaphragmatic pressure (Pdi) which is the difference between abdominal pressure (Pab) and pleural pressure (Ppl). Pab and Ppl are measured using balloon catheters inserted in the stomach and lower third of the esophagus, respectively. Isometric contraction of the diaphragm was assured by binding the lower chest and abdomen with a cast. Blood flow to the diaphragm was measured using a Doppler flow probe of appropriate size around the left phrenic artery.[6] Two groups of animals were used: NON-STIM (n=7), control TOF measurements of the diaphragm were made and vecuronium (.04 mg/kg) administered after a 2-3 min stimulation-free period; STIM (n=6), the same loading dose of vecuronium was administered after a 2-3 min period of TOF stimulation. Stimulation of the diaphragm was started no earlier than 30 sec after muscle relaxant administration in the NON-STIM group. Measurements included: phrenic artery blood flow; time to 25, 50, 75% and maximal first twitch depression; time to 25, 50 and 75% twitch recovery; and percent of maximal twitch depression. All values are expressed as mean ± standard error of the mean (SEM). Comparisons were made using paired Student's t test. A p .05 was considered statistically significant.

Results.

Although blood pressure, cardiac output, temperature and acid base status were not different between groups, phrenic artery blood flow increased from 2.2 ± 0.46 in the NON-STIM to 8.28 ± 1.7 ml/min in the STIM group ($p \leq .001$). Onset times to 25-50-75% and maximal twitch depression were: 92 ± 5, 115 ± 7, 148 ± 9 and 249 ± 18 in the NON-STIM group and 33 ± 2, 42 ± 3, 55 ± 2 and 82 ± 8 sec in the STIM group. All data were statistically different ($p \leq .001$). Recovery times were not statistically different between the two groups. Maximal twitch depression was 11 ± 4.1% of control in the NON-STIM group and 0.08 ± 0.06% of control with TOF stimulation.

Discussion.

This study shows that TOF stimulation of the diaphragm prior to administration of loading doses of vecuronium is accompanied by a three-fold reduction in onset times and a more complete diaphragmatic relaxation. These pharmacodynamic changes were associated with a three-fold increase in phrenic artery blood flow. Furthermore, we found no significant changes in recovery times with TOF stimulation. This study confirms the effects of TOF stimulation on neuromuscular blockers (NMB) and why it should be avoided when studying NMB onset times. It also gives an order of magnitude as to the expected blood flow changes with TOF. It would be of interest to study if other muscles are affected to the same degree by TOF stimulation and if other modes of stimulation also have an effect on blood flow and NMB pharmacodynamics. There is no standard in muscle relaxant research as to the duration of muscle stimulation prior to drug administration. Since this will affect the characteristics of drug action, standardization is imperative. One possible protocol that would reduce the effect of muscle blood flow and would allow us to study each drug's intrinsic activity is used and described in this abstract.

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TITLE: DOES ACUTE NORMOVOLEMIC HEMODILUTION SAVE BLOOD?

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Introduction. Acute normovolemic hemodilution (ANH) entails collecting a patient's blood immediately before surgery with concurrent fluid infusion to maintain intravascular volume. This reduces the red cell mass (RCM) lost during surgery by lowering the hematocrit (Hct) at which surgical blood loss (SBL) occurs. Blood collected during ANH is later reinfused to replace the red cell losses that do occur during surgery. In theory, the total amount of RCM loss at the end of surgery should be less with ANH than without it. Advocates for this technique claim that it can be used to reduce or eliminate homologous blood transfusion during surgery [1-3]. To evaluate this claim, we developed a mathematical model that compares the RCM saved when ANH is used with RCM loss when ANH is not used.

Methods. The model is based on the following mass balance relation:

$$RCMf = RCMi - RCMl + RCMt,$$

where f = final (after blood loss), i = initial (before blood loss), l = lost, and t = transfused. The model assumes: (1) total blood volume remains constant, (2) ANH occurs prior to SBL, (3) reinfusion is concurrent with SBL cc for cc, (4) reinfusion starts with the most dilute of the units collected during ANH, and (5) SBL is equal to the total volume collected during hemodilution. The patient is 70 kg with an initial Hct of 40 and total blood volume of 4900 cc (70 cc/kg). Each unit collected contains 450 cc of the patient's blood and 63 cc of anticoagulant.

Results. Hematocrit was higher with ANH than without it; this difference was progressively greater as hemodilution increased. However, large volumes of red blood cells were not saved by using ANH (Table). Given that a unit of packed red cells contains a red cell volume of 150 cc (250 cc, Hct = 60), one would have to remove 7 units by ANH, which would result in an Hct of 20.9, to salvage the equivalent RCM for this patient.

Discussion. This model is designed to ensure that blood salvage is maximal by diluting the blood to whatever is deemed the minimal "safe" Hct prior to SBL. Retransfusion must begin at the start of SBL to avoid a decrease in Hct below the "safe" level. If SBL exceeds the volume collected by ANH, the HCT after ANH would be less than that predicted by the model. If SBL were less than the collected blood volume, the Hct after ANH would be greater than that predicted by the model; but replacement with solutions that do not contain red blood cells would likely maintain a "safe" Hct. This model suggests that ANH is minimally efficacious for red cell mass salvage and minimizing homologous red cell transfusion.

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Table. Final Hematocrit (Hct) after Surgical Blood Loss (SBL) with and without Acute Normovolemic Hemodilution (ANH) According to a Mathematic Model

	Units of Blood Removed						
	4	5	6	7	8	9	10
SBL	2052	2565	3078	3591	4104	4617	5130
Hct with ANH	28.4	26.7	25.2	24.1	23.1	22.3	21.7
Hct without ANH	27.7	25.2	23.0	20.9	19.2	17.5	16.0
Net red blood cells saved (cc)*	35	70	109	150	194	238	282

*Net red blood cells = [(Hct with ANH) - (Hct without ANH)] x total blood volume.

Title: EFFECTS OF VERAPAMIL, NIFEDIPINE AND NIMODIPINE ON A CAT SOLEUS NEUROMUSCULAR PREPARATION

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Introduction. Recently, nimodipine (Nim) has been employed to minimize neuronal injury after ischemia (1,2) and subarachnoid hemorrhage (3,4). However, verapamil (Ver), a calcium channel antagonist (CCA), reportedly inhibits neuromuscular function (5,6). Therefore, this study was designed to assess the effects of CCA's (Ver, Nim, and nifedipine (Nif)) on the neuromuscular junction.

Methods. With permission from our institutional animal care comittee, experiments were performed on anesthesized cats weighing between 1.75 - 3.8 kg (N=36). Anesthesia was induced with nitrous oxide and halothane and maintained with alpha-chloralose. The cats were ventilated to maintain normocarbia. Arterial BP, end tidal CO_2 and ECG were monitored continuously. Cat soleus neuromuscular preparations were like those of Standaert (7) and Riker (8). Intravenous (iv) and intraarterial (ia) injections were via a cephalic vein and ipsilateral popliteal artery, respectively. The isometric contractile tension of soleus muscle in response to supramaximal stimuli at 0.4 Hz was recorded. Intermittent tetanic stimulation at 400 Hz • 10 sec. evokes a neurogenic post-tetanic repetition and twitch potentiation (PTP)(7,8). Twitch and PTP (both the result of indirect stimulation) were used to assess the effects of Ver (10 - 2000 mcg/kg iv, 100 - 800 mcg/kg ia), Nim (100 - 500 mcg/kg iv), and Nif (100 - 500 mcg/kg iv, 100 - 200 mcg/kg ia) on the neuromuscular junction.

To assess the effects of these drugs directly on the muscle, curare was titrated to ablate indirect twitch entirely (N=6). The CCA's were then administered while the soleus muscle was stimulated directly.

Results. Ver, as a function of dose, potentiated the indirect twitch response and inhibited PTP. Ver does not affect muscle response to direct electrical stimulation.

Nim did not effect indirect twitch nor PTP (8 of 9 preps). Nim occassionally (4 of 11 preps) and transiently enhanced direct twitch.

Nif occassionally enhanced indirect twitch (3 of 14) and inhibited PTP (4 of 10, aver = 15%). Nif increased direct twitch by 20%.

Discussion. The CCA's examined had minimal effect on neuromuscular transmission. Our findings are in fairly good agreement with those of Sato and Ono (9). Differences in muscle type examined, electrolyte and metabolic imbalances and administration of other drugs known to inhibit neuromuscular function could explain the discrepency our findings with that of other authors (5,6,10,11). Alpha-chloralose, used in our preparations, does not effect the pre or post junctional activity of the neuromuscular junction (NMJ) (12). Thus, our results represent the effects of CCA's on the NMJ of a fast twitch muscle (soleus) and not their effects in the presence of other confounding factors. Therefore, patients with nondepressed normal functioning NMJ should tolerate the administration of CCA's without deterioration of skeletal muscle function. However, administration of CCA's to an abnormal NMJ may result in enhanced weakness (6). In addition, co-administration of CCA's with other NMJ depressants may result in augmented NMJ depression while the administration of either alone may have been clinically benign (ie. the simultaneous use of a CCA and a defasciculating dose of curare may provoke dyspnea and/or apnea)(5,6,10,11) .

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Title:

NITROUS OXIDE SELECTIVELY RELEASES MET(5)-ENKEPHALIN INTO CANINE THIRD VENTRICULAR CEREBROSPINAL FLUID

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Introduction: Previous work regarding mechanisms of nitrous oxide (N_2O)-induced analgesia includes a body of indirect pharmacological evidence suggesting an interaction between N_2O and the opioid receptor - endogenous opioid peptide (EOP) system[1]. To obtain more direct evidence of this possible interaction, we measured concentrations of five naturally occurring EOPs in samples of cerebrospinal fluid (CSF) obtained from chronically cannulated 3rd ventricles of dogs with the animals breathing either room air or 66-75% N_2O in oxygen through a face mask.

Methods: This study was approved by the Institutional Animal Care and Use Committee. Eight conditioned mongrel dogs, weighing 9-11 kg, trained to lie quietly in the laboratory and accept a face mask, were anesthetized with pentobarbital, 36 mg/kg, iv, and breathed room air spontaneously through an endotracheal tube. Under aseptic conditions, a custom made, heparin-bonded, silicone rubber catheter (ID=0.3 mm) was inserted through a custom made 19 gauge stainless steel guide cannula with its tip stereotactically implanted through a burr hole into the third cerebral ventricle (coordinates: midline, AP -16 mm), such that the tip of the catheter extended 3-5 mm beyond the tip of the guide cannula. The latter was fixed to the skull using bone screws and methacrylate cement and the silicone catheter was affixed to the guide cannula using silicone cement. The external end of the catheter was plugged until use. No less than 48 hours after surgery, each animal, restrained only by a short leash, was randomly given either room air (control) or 66-75% N_2O in oxygen (experimental) to breathe through a face mask via a nonrebreathing system. The external end of the catheter was connected via sterile polyethylene tubing to a Harvard withdrawal pump and CSF was removed at a rate of 1.5-1.9 ml/hr. When a sufficient quantity of CSF had been obtained, either the inspired mixture was changed and additional specimens of CSF were collected or the catheter was replugged for use on a further day. After volume measurement, CSF specimens were transferred to polypropylene tubes and placed in a boiling water bath for 10 min, centrifuged at 1000xg for 10 min and supernatants frozen at -70°C until EOP analysis. Specimens were coded such that the circumstances under which each had been obtained (F_IN_2O = 0 or 0.66-0.75) was not known until after peptide analysis was completed. For peptide analysis, CSF samples were thawed and passed through Sep-Pak C18 cartridges (Waters) which had been pretreated with acetonitrile (CH_3CN) and water. The cartridges were washed with 5ml 0.05M PO_4 buffer, pH 2.7, and EOPs eluted with 2ml of 40% CH_3CN in PO_4 buffer. Eluates were taken to dryness under reduced pressure and reconstituted in 200 ul of water for analysis of EOPs. Physical separation of 5 naturally occurring EOP's (met^5-enkephalin (ME), leu^5-enkephalin (LE), beta-endorphin (BE), met^5-enkephalin-arg^6-phe^7 (MERF) and dynorphin A (DYN-A)) was performed by reversed phase high performance liquid chromatography (HPLC) on a Hewlett-Packard 1084B liquid chromatograph equipped with fraction collector using a Microsorb 3 micron, C18, 10cm analytical column and guard column (Rainin Instruments) in a gradient of CH_3CN and 0.05M PO_4 buffer containing 0.1% triethylamine going from 15 to 50% acetonitrile at a flow rate of 0.5 ml/min over 42 minutes. Fractions of column effluent bracketing the known elution times of each authentic peptide run under the same chromatographic conditions were collected, taken to dryness under reduced pressure, and reconstituted in a volume and type of buffer appropriate for radioimmunoassay (RIA) of each of the five peptides using commercially available kits. All samples from the same dog were measured using the same RIA kit for each peptide. Mixtures of authentic peptide standards were also analyzed under identical conditions for determination of EOP recovery. EOP concentrations in control and experimental CSF samples were compared using paired Student's t-test.

Results: ME concentrations ranged from less than 0.13 to 0.44 picomols/ml CSF in dogs breathing room air and were significantly increased (P=0.0015) when breathing N_2O, ranging between 9.6 and 52 pmols/ml. MERF was also increased (P=0.037), from 3.2-18.8 pmols/ml while breathing air, to 1.7-115 pmols/ml in the presence of N_2O. Concentrations of LE, BEND and DYN A were unchanged, ranging overall from 34-134, 24-6000, and 0.04-1.9 pmols/ml CSF, respectively.

Discussion: These results provide direct evidence of an interaction between N_2O and the EOP system, explaining the partial antagonism of N_2O analgesia by narcotic antagonists.[1] In addition, these results are among the first demonstrating a selective alteration among EOP systems.

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Title: NONANESTHETIC ALCOHOLS DISSOLVE IN TADPOLES AND SYNAPTIC MEMBRANES WITHOUT DISORDERING LIPID

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Introduction: General anesthetics (GAs) are a heterogeneous group of substances for which few structural requirements are known. One which has been identified is found in the homologous series of n-aliphatic alkanols, where members with fewer carbons than tridecanol can produce anesthesia, but those with more than 13 carbons are inactive (1). This "cutoff" in potency might be explained by either failure of the nonanesthetics to achieve a sufficient concentration at the site of action (2), or loss of intrinsic efficacy beyond tridecanol (3). To distinguish between these possibilities, uptake of even-numbered primary alkanols from octanol through octadecanol into purified postsynaptic membranes, was measured by a radiotracer method.

Methods: Alkanol uptake into membranes was determined in postsynaptic membrane fragments purified from electric organ of Torpedo by differential and sucrose density gradient centrifugation (4). (Such membranes are structurally and biochemically like those derived from central nicotinic synapses, but can be obtained with greater purity and abundance). In most experiments, 1 ml of membrane suspension (8.8 mg protein) was mixed with 10 Ml of an ethanolic stock solution of each ^{14}C-labeled alcohol. The mixtures were then layered on continuous sucrose gradients (0.8 - 1.4 M sucrose), centrifuged to equilibrium (64,000 x g, 4 hr, 4°C), and then fractions collected and assayed for protein and alcohol content.

Alkanol uptake into tadpoles (Rana pipiens) were measured after exposure to saturated aqueous solutions of each ^{14}C-alkanol (ICN, Irvine, CA, or New England Nuclear, Boston, MA) for up to 92 hours. Animals were then sacrificed, weighed, dissolved in BTS-450 (Beckman, Fullerton, CA), and alkanol contents assayed by scintillation counting.

Lipid perturbations were monitored by electron spin resonance spectroscopy. Postsynaptic membranes were spin labeled by gentle shaking (6 hr, 4°C) with a spin probe (12-doxylstearate) previously deposited from methanolic stock solution. Probe concentration was < 1% of membrane lipids (mol/mol). Membranes were then washed (three cycles of 6,000 x g for 10 min each, 4°C) and resuspended to minimize signal distortion from unbound spin label. Small aliquots (<25 Ml) of ethanolic stock solutions of each ^{14}C-alkanol were added to 250 Ml of spin labeled membranes (4 mg/ml protein), incubated (room temperature, 30 min), washed free of ethanol, and sealed into glass capillary tubes. ESR spectra were obtained on a Bruker ER200 spectrometer operating at 9.5 GHz with 10 mW of microwave power. Following spectroscopy, samples were sedimented (6,000 x g, 15 min) and the supernatants discarded. The pellets were then dispersed in scintillation cocktail and the membrane ^{14}C-alkanol contents determined.

Results: After equilibrium sedimentation, all radioactivity loaded onto the sucrose density gradients was exclusively associated with membrane-containing fractions for ^{14}C-decanol and higher molecular weight ^{14}C-alkanols. (In peak fractions, alkanol contents were estimated to be as high as 70 mM in the lipid bilayer). In contrast, ^{3}H-sucrose was distributed throughout all fractions of its gradient.

^{14}C-alkanols were also taken up by tadpoles. For example, at the anesthetic concentration, tadpoles were found to contain 0.4 mmoles of ^{14}C-dodecanol/kg wet weight. In contrast, after 92 hours of exposure to a saturated solution of ^{14}C-tetradecanol, tadpoles were found to contain 0.7 mmoles/kg wet weight, but such high concentrations still failed to produce anesthesia as measured by loss-of-righting reflex assay (performed as described in (5)).

Since nonanesthetics could dissolve in both synaptic membranes and in intact animals, intrinsic lipid disordering efficacies of the alkanols were tested by ESR spectroscopy. It was found that all of the anesthetic alkanols disordered membrane lipid as a linear function of concentration in the membrane, but disordering efficacy progressively declined among the higher members of the series such that nonanesthetics either failed to disorder, or actually ordered membrane lipid. Specifically, when the change in lipid order parameter (from the control value) is plotted as a function of membrane alcohol mole fraction, the slopes (± standard errors) for least squares fits constrained to pass through zero were: octanol, -0.39 ± 0.029; decanol, -0.27 ± 0.026; dodecanol, -0.13 ± 0.015; tetradecanol, -0.03 ± 0.018; hexadecanol, +0.11 ± 0.034; and, octadecanol, +0.36 ± 0.071.

Discussion: Despite achieving concentrations in synaptic membranes in excess of those usually associated with anesthesia, long chain alkanols beyond (but including) tetradecanol, both failed to produce anesthesia and were unable to disorder membrane lipids. Indeed, the slope of the lipid order parameter vs. alkanol membrane concentration relationship for tetradecanol was not different than zero ($p > 0.1$), and those for hexadecanol and octadecanol were even greater than zero ($P < 0.01$). Thus, lipid disordering in Torpedo postsynaptic membranes accurately predicts the position for the anesthetic potency "cutoff" among the primary alkanols acting in the tadpole's central nervous system. This supports a lipid perturbation mechanism of anesthetic action.

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GM35900, GM15904, and the Department of Anaesthesia, MGH. LLF was a Fellow of the King Trust, Boston, MA.

Title: THE EFFECT OF CYCLOSPORINE ON THE POTENCIES OF GENERAL ANESTHETICS

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Introduction: Cyclosporine is an immunosuppressive agent which has revolutionized the clinical practice of organ transplantation. At therapeutic concentrations, cyclosporine readily crosses the blood-brain barrier and can produce seizures and coma in man. Recently, other central effects of cyclosporine have been demonstrated, including prolongation of the sedating actions of barbiturates and potentiation of narcotic-induced analgesia (1), and attenuation of the opiate withdrawal syndrome (2). Considering these provocative interactions with centrally-acting drugs, and the steeply increasing proportion of surgical patients under treatment with cyclosporine, we investigated the reversible central effects of physiological concentrations of cyclosporine on anesthetized animals. Specifically, we tested the hypothesis in mice that cyclosporine diminishes the requirement for general anesthetics (GA).

Methods: Institutional approval for animal use was obtained from the IACUC. The endpoint of loss-of-righting reflex was examined in Charles River CD-1 male mice at 37^{o} for halothane and enflurane. Briefly, eight 26-34g mice were placed in individual cages mounted on a carousel enclosed in a gas-tight chamber. Anesthetic vapors were diluted in O_2, and gas inflow rate (5 L/min) was sufficient to maintain O_2 at the desired chamber concentration (>50%), CO_2 <1%, and balance N_2. After allowing 30 minutes for equilibration, the carousel was rotated at 4 rpm and mice which passively rolled over twice were scored for loss-of-righting reflex. Studies were repeated several times and data pooled. Median effective concentrations were then computed according to the method of Waud (3) for quantal responses. Two hours prior to assays, control groups were injected intraperitoneally with 0.3cc vehicle (cremophor), while experimental groups received the same volume of a cyclosporine-containing solution in vehicle (Sandimmune, Sandoz) resulting in administration of 50 mg/kg. Concentrations of GA vapors and the gases were monitored with an Ohmeda 6000 mass spectrometer.

Results: Vehicle-treated control mice are compared to the cyclosporine-treated group in Table 1. For both GA agents, cyclosporine failed to reduce the EC50 to a statistically significant degree.

Discussion: Cyclosporine is a lipophilic, cyclic undecapeptide. Its known biological activities are strongly related to its lipophilic properties. Cyclosporine's subcellular site of action is still unknown, and although a specific cytosolic receptor protein has been identified in certain tissues including brain, it is also known to partition into bilayers. Thus, there is the possibility that some or all of cyclosporine's actions are "nonspecific", as seems to be the case for the GAs.

Recently, it was demonstrated (1) that in mice, a single dose of cyclosporine (60 mg/kg IM) could prolong the "sleep time" for a single dose of pentobarbital, as well as enhance the analgesic effect of a single dose of fentanyl in a dose-dependent manner. Previous studies in rodents had shown that any conventional route of administration (i.e., IV, IM, SQ, IP) could result in substantial cyclosporine levels in CSF and brain tissue, and thus an interaction in the CNS between cyclosporine and these drugs, was proposed. Unfortunately, plasma levels of pentobarbital were not measured, nor were inhalational GAs tested, and thus it is impossible to tell whether cyclosporine's obtunding effects were pharmacokinetic (e.g., caused by delaying drug elimination or altering drug distribution), or, pharmacodynamic (caused by an alteration in potency or efficacy at the anesthetic site of action). Our data demonstrated that cyclosporine itself (at the doses administered in this study) does not produce obtundation, nor does it produce a significant diminution in the requirement for volatile GAs in mice. Such findings indicate that the reported prolongation of hypnotic effects are probably due to pharmacokinetic effects of cyclosporine rather than actions at the GA site.

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Table 1.

	CONTROL			+CYCLOSPORINE			P***
	EC50*	±SE	n**	EC50	±SE	n	
ENF	0.98	0.04	60	0.91	0.05	60	> 0.3
HAL	0.64	0.04	48	0.57	0.04	46	> 0.2

* EC50 is expressed in % atmospheres.

** 'n' represents the total number of mice studied.

*** The estimated variance in EC50 for paired groups was calculated from the standard errors; the sum of these then yielded the estimated variance of the difference in EC50 between treated and untreated mice anesthetized with the same agent. The ratio of this difference to its standard error was then referred to a standard normal distribution.

Supported by the Department of Anesthesiology and CCM, University of Pittsburgh. Cyclosporine was generously provided by Sandoz.

Title: ANTINOCICEPTIVE EFFECTS OF INTRATHECAL DEXMEDETOMIDINE IN RATS

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Introduction: Dexmedetomidine (DMET) is a potent and highly selective alpha-2 adrenergic agonist that has recently been shown to reduce anesthetic requirements by greater than 90%.[1] Spinal alpha-2 adrenergic receptors have been shown to modulate nociceptive processing.[2] The present study examined the antinociceptive properties of dexmedetomidine when given intrathecally (IT) in rats.

Methods: Following approval by the institutional Animal Care Committee, 24 male Sprague-Dawley rats weighing 250-300 g were anesthetized with 2% halothane. PE 10 catheters were inserted into the subarachnoid space via an incision in the atlanto-occipital membrane and advanced 8 cm caudally to the level of the lumbar enlargement. The proximal end of the catheter was externalized percutaneously and sealed with 28 gauge wire. The animals were allowed to recover for a minimum of 48 hours at which time they were examined and any animal with evidence of a neurologic deficit was excluded from further study. Control measurements were made of response latencies on the 52.5° Hot Plate (HP) and Tail Flick (TF) tests as previously described.[3] Animals then received in a blinded and random fashion, an IT injection of 10 µl of saline or an equal volume of saline containing 1, 3, or 10 µg of DMET (6 animals per group). The catheter was flushed with 10 µL of saline following which HP and TF latencies were determined at 5, 15, 30, 60, 90, 120, and 180 minutes post-injection. Cutoff times were 60 and 6 seconds for HP and TF latencies respectively. Results are expressed as Maximum Percent Effect (MPE) which was calculated by the following formula : MPE=(Postdrug Latency - Predrug Latency) / (Cutoff - Predrug Latency). In a separate series of experiments, 6 rats received 10 µg of DMET IT followed 15 min later by either 30 µg of the alpha-2 antagonist idazoxan or saline. HP and TF latencies were recorded at 5, 15, 30 and 60 min post-administration of the idazoxan. Data were analyzed using a 2-way ANOVA followed by Dunnett's test for multiple comparisons *vs.* the saline group where indicated.

Results: IT administration of 3 or 10 micrograms of dexmedetomidine resulted in a significant increase in HP latencies which were maximal within 5-15 minutes of injection (Figure 1). In those animals that received 3 µg of DMET, HP latency had decreased to the control value by 180 min post-injection. In animals which received 10 µg of DMET, HP latencies remained at 49% of MPE even at 180 min post-injection. Animals receiving 1µg of IT DMET showed no significant differences from the saline group. A maximal increase in TF latency was seen within 15 min of IT administration of DMET (Figure 2). 100% MPE were observed in animals receiving either 3 or 10 µg of DMET. MPE decreased to baseline values over the ensuing 120-180 minutes. Administration of IT idazoxan reversed the antinociceptive effects of DMET. Animals which received 10 µg of DMET displayed decreased spontaneous movement but motor function and the righting reflex were preserved.

Discussion: This study demonstrates that the IT administration of the alpha-2 adrenergic agonist DMET can produce significant analgesia as evidenced by increased HP and TF latencies. This analgesia could be reversed by the alpha-2 antagonist idazoxan. These results provide further evidence that the spinal administration of agents which act at the alpha-2 adrenergic receptor may be useful in the control of acute pain.

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HOT PLATE

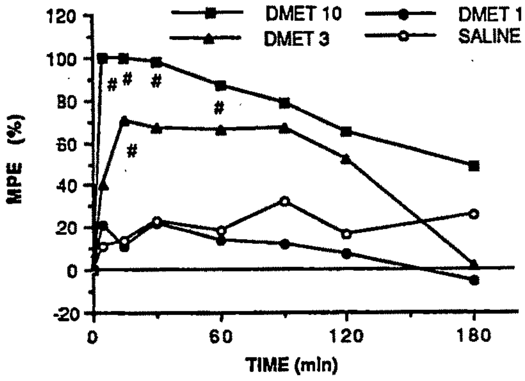

Figure 1. Hot Plate latency following the intrathecal administration of saline, 1,3, or 10 µg of DMET. #=p<0.05 *vs* .saline.

TAIL FLICK

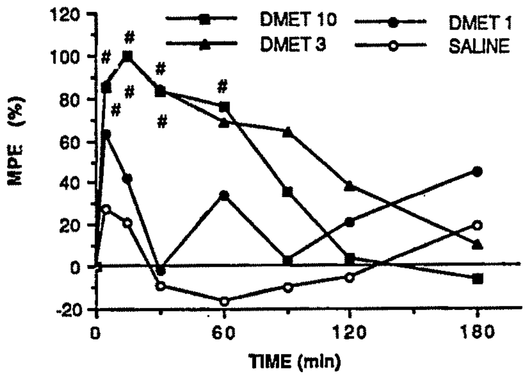

Figure 2. Tail Flick (TF) latencies following the intrathecal administration of saline, 1,3, or 10 µg of DMET. #=p<0.05 *vs.* saline.

TITLE: PREDICTING DIFFICULTY IN VENTILATING INFANTS WITH TRACHEOESOPHAGEAL FISTULA

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Introduction: Several reports exist in the surgical and anesthesiology literature documenting ventilation disasters or near disasters in the management of the infant with esophageal atresia(EA) and tracheoesophageal fistula(TEF) after gastrostomy. Although some have clearly documented intubation of the fistula as the cause of difficulty (1), others have speculated that a decreased pulmonary compliance is the most common etiology(2,3), both leading to an increased flow of ventilating volumes through the fistula and out the vented stomach. No large study has come forth with objective criteria for predicting difficulty in ventilating the infant with TEF.

Methods: A retrospective chart review in which patients with TEF who were admitted to the University Hospital during the period from 1970 to 1985 were enrolled. A detailed review of the ICU, respiratory therapy, anesthetic, operative, and laboratory records was undertaken in an effort to document the frequency, severity, and specific situations in which ventilation in this select group of patients was compromised.

Results: Included in the study were 55 infants, 53 presenting with proximal EA and distal TEF and 2 presenting with the H-type fistula. These 55 patients underwent 78 anesthetics in which 24 had a staged repair of the TEF and EA after initial gastrostomy while 31 had a complete repair at the initial procedure. In infants with EA and TEF, sudden respiratory embarrassment(SRE) as judged by the sudden development of respiratory acidosis on blood gas analysis($pH < 7.30$ & or $pCO_2 > 50$) and or sudden loss of ventilatory volumes and pressure, occurred in 8/53(15%) of patients at gastrostomy and in 11/53(21%) at thoracotomy. In all, 17/53(29%) experienced SRE at either procedure. In all instances the patients were intubated and under controlled ventilation at the time. In no instance did a full cardiorespiratory arrest occur.

Weight was highly predictive of SRE at gastrostomy or thoracotomy with those less than 2000 grams experiencing SRE in 75%(n=8) of cases and those greater than 2000 grams in only 24%(n=45) of cases,($p < .01$). Gestational age was also of predictive value as those less than 34 weeks experienced SRE 100%(n=5) of the time and those greater than 34 weeks, 25%(n=48), ($p < .01$). Peak inspiratory pressure(PIP), was 24 ± 5 cmH20 (n=10) at thoracotomy and 24 ± 10 cmH20 (n=7) at gastrostomy in the SRE group while 22 ± 5 cmH20 (n=18) at thoracotomy and 25 ± 5 cmH20 (n=18) at gastrostomy in those not experiencing SRE. PIP was therefore of no predictive value.

Discussion: The creation of a gastrostomy in the patient with proximal EA and distal TEF may, as has been reported previously, cause sudden respiratory embarrassment from loss of ventilatory pressure, and could at times be fatal. In addition, we have found that SRE is frequently encountered in the lateral position during thoracotomy for fistula ligation in infants in whom a gastrostomy has been previously created.

Although SRE occurs with much greater frequency in the smaller and more premature infant, we have not found it to correlate with the severity of pulmonary disease and altered compliance as reflected by PIP. The Hagen-Poiseuille equation: $Q = \pi (R)^4 \Delta P/8u$, where Q =flow across the fistula, R = radius of the fistula and P = (P airway - P intragastric), describes the factors involved in determining the degree of volume loss across the fistula. With gastrostomy, P intragastric = P atmosphere $\cong 0$. Although decreased pulmonary compliance, reflected in an elevated PIP $\cong$ P airway, would increase volume loss across the fistula we found little difference in PIP between those who did and did not develop SRE. Therefore, it may be the size of the fistula, or its radius(R), which is more important in determining volume loss across the fistula. The effective radius of the fistula is determined not only by its inherent size but also by intermittent partial occlusion from an endotracheal tube. The importance of the radius and any changes in the radius in determining flow across the fistula is emphasized by the 4th power to which this factor, (R), is taken in the Hagen-Poiseuille equation.

In spite of the above, why is it that SRE is experienced with greater frequency in the smaller and more immature infant? It is easy to see that proper positioning and maintaining the position of the endotracheal tube may be more difficult in the smaller infant. Secondly, it may be that the size of the fistula relative to the child's weight and thus the flow across the fistula relative to tidal volume or minute ventilation may be greater in the smaller infant. In addition, the premature infant, with immature lungs, regardless of whether it is reflected by a significantly increased PIP, combined with an increased metabolic rate relative to his older counterpart, is less likely to tolerate even small perturbations on its ventilatory equilibrium.

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Title: THE SITE AND MECHANISMS OF TETANIC FADE IN THE ABSENCE OF NONDEPOLARIZING MUSCLE RELAXANTS IN RATS

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Introduction. It is generally accepted, that in the presence of low concentrations of d-tubocurarine (d-Tc) or that of other nondepolarizing muscle relaxants (MR), which only cause a small decrease of the force of contraction (P) at low (< 1 Hz) stimulation rates, tetanic fade is caused primarily by inhibition of the mobilization of acetylcholine (ACh) from reserve stores to release sites (1,2). The site and mechanism of the tetanic fade in the absence of nondepolarizing MR, has not been investigated. In the present study the decay of tetanic tension P_t of the indirectly and directly stimulated muscles was compared in in vitro and in vivo experiments in the presence and absence of MR.

Methods. The experiments, approved by the Institutional Animal Investigation Committee, were carried out in vitro on the phrenic nerve - hemidiaphragm and in vivo on the sciatic nerve - tibialis anterior preparation of male Sprague-Dawley rats. The hemidiaphragms were suspended in modified Krebs' solution ($[CaCl_2]$ = 1.4 mM/ $[MgSO_4]$ = 0.9 mM), aerated with 95% O_2-5% CO_2, temperature 37°C, pH 7.38-7.42. In the in vivo experiments rats were anesthetized with i.p. pentobarbital and urethane tracheostomized and mechanically ventilated with O_2. Both in vitro and in vivo preparations were stimulated indirectly, via the corresponding nerve, or directly with needle electrodes inserted into the muscle, with supramaximal square wave impulses of 0.2 or 2.0 ms duration during indirect and direct stimulation, respectively, either at 0.1 or at 50 Hz. In experiments with direct stimulation, the indirect component of direct stimulation was eliminated (3), by blocking neuromuscular (NM) transmission with d-Tc in vitro and the continuous infusion of vecuronium in vivo. P and P_t were quantitated with FT03 transducers and recorded. At first control values of P were determined at 0.1 Hz. Subsequently 50 Hz tetani were applied until P_t decreased to less than 50% of its initial value.

Results. The observations illustrated in the figure and summarized in the table indicate that there is no difference in the magnitude of the P_t/P ratio and in rate of tetanic fade as measured by the time (sec) required for P_t to decrease to 50% of its initial value (TF50) during indirect or direct stimulation, either in vitro or in vivo.

Discussion. During direct stimulation of a completely curarized NM preparation, muscular contraction is initiated by depolarization of the electrosensitive muscle fiber membrane by an exogenous current. ACh released by the nerve impulse plays no role in this process. Under these circumstances the decay of tetanic tension can not be the consequence of the inhibition of the mobilization of ACh but must be due to the exhaustion of the contractile mechanism of the muscle fiber. The finding that there was no difference, either in vitro or in vivo in tetanic fade during indirect and direct stimulation suggests, that in the absence of nondepolarizing MR, tetanic fade, even during indirect stimulation, is caused by the exhaustion of the contractile mechanism and not by the depletion of the readily available ACh stores. This assumpton is supported by the 5 to 10 fold safety margin of ACh release (4). It appears that when all postjunctional cholinergic receptors are free to interact with ACh and the mobilization of ACh is not inhibited, the contractile mechanism of the muscle will fail sooner, under prolonged high frequency stimulation, than NM transmission. Otherwise tetanic fade would be expected to occur earlier during indirect than during direct stimulation.

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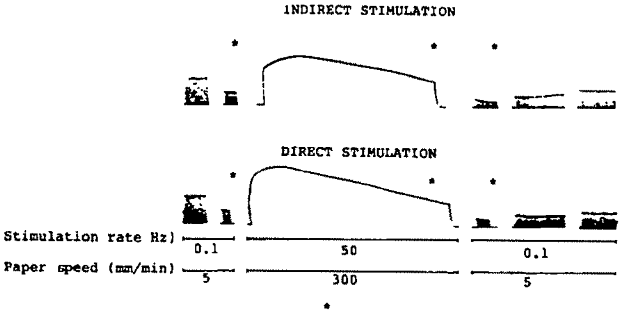

*Sensitivity of recorder halved

Rat phrenic nerve hemidiaphragm preparation. Note that tetanic fade during direct and indirect stimulation is similar.

Twitch tension (P), tetanic tension (P_t) and time to 50% tetanic fade (TF50)

	In Vitro		In Vivo	
	Indirect (n=8)	Direct (n=6)	Indirect (n=10)	Direct (n=8)
Parameters	Stimulation		Stimulation	
P	100	100	100	100
P_t	414±31*	379±8	346±8	394±8
TF50 (sec)	23.6±1.5	22.0±1.7	18.2±0.8	18.0±2.0

*Means±SEM of n; P_t expressed as % of P.

Title: PHARMACOKINETICS OF INTRAMUSCULAR METHOHEXITAL IN CHILDREN

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Introduction. Young children who require diagnostic radiologic procedures, such as computerized tomography or magnetic resonance imaging, often have great difficulty cooperating and remaining completely immobile during the period of time required to complete the scan. When this type of situation arises, patient movement can produce artifacts that result in a non-diagnostic scan. In addition, the schedule delays that occur adversely affect the efficiency of the radiology department. Consequently, many of these children require sedation or general anesthesia to allow successful completion of their diagnostic procedure. Although many drugs have been used to provide sedation in this clinical situation, most are associated with significant complications.[1-3]

Intramuscular administration of methohexital has been shown to be a safe, effective method of sedating children for CT scanning; however, it is not always successful.[4,5] Many factors may influence the absorption of methohexital and the plasma concentrations achieved following administration of the drug, but the pharmacokinetics of intramuscular methohexital in children have not been evaluated. Therefore, the purpose of this study was to determine plasma methohexital concentrations in children following intramuscular administration.

Methods. Eight ASA I or II children who required magnetic resonance imaging were studied after obtaining informed parental consent to the institutionally approved protocol. Each child received 10 mg/kg of a 5% methohexital solution administered intramuscularly. Parents remained with their children until the onset of sleep which was defined as loss of consciousness, unresponsiveness to verbal stimuli and absence of voluntary movement when unstimulated. Time from administration of the drug until the onset of sleep was recorded. After each child was asleep an intravenous catheter was placed and the scanning procedure was completed. Blood samples were collected during the scan at 15, 30, 45 and 120 minutes following drug administration. The samples were centrifuged and the plasma frozen for later determination of methohexital concentrations using gas chromotography. If additional sedation was required during the course of the procedure, intermittent doses of intravenous ketamine were administered. Results are expressed as mean ± SD.

Results. Seven children were asleep within five minutes (mean 3.1 ± 0.8 min). One child required additional sedation with ketamine prior to beginning the procedure. The magnetic resonance imaging procedures lasted 22-90 minutes (mean 49 ± 22 min) and seven children required supplemental medication during the procedure to maintain immobility. The plasma methohexital concentrations achieved following intramuscular administration of the drug are shown in Figure 1. No adverse effects were encountered.

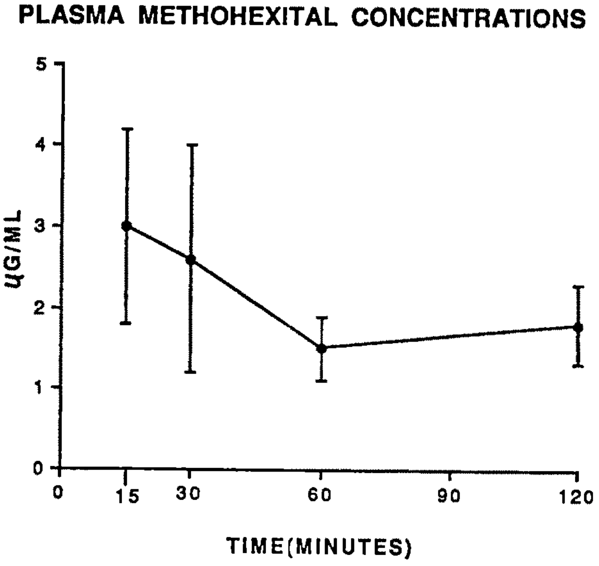

Figure 1

Discussion. In this study 87% of patients fell asleep within five minutes of receiving intramuscular methohexital (10 mg/kg). This is consistent with the results of earlier studies.[4,5] In the majority of patients additional sedation was required during the course of the procedures, which lasted up to ninety minutes. Following the procedure recovery was prompt and uncomplicated. We conclude that plasma methohexital concentrations achieved following intramuscular methohexital produce safe, effective sedation in children undergoing diagnostic radiologic procedures.

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Title: METHOHEXITAL ANESTHESIA FOR CARDIOVERSION
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Introduction-Patients undergoing synchronized electrical cardioversion for atrial flutter or fibrillation require an anesthetic characterized by rapid emergence and hemodynamic stability. Many intravenous anesthetics have been used, including diazepam, thiopental, etomidate, and propofol.[1,2,3] Despite successes, their disadvantages are evident. Recall and prolonged sedation are a problem with diazepam.[1] Thiopental has a prolonged elimentation half life of 12.0 ± 5.5 hrs, and may precipitate hypotension. Hypotension may be a greater problem with propofol, compared to thiopental, especially in elderly patients or those with coronary artery disease.[4] Etomidate may cause myoclonus, which interferes with cardioversion and electrocardiogram (ECG) interpretation[3]. Methohexital, an oxybarbiturate, has an elimination half life of only 3.9 ± 2.1 hrs, with more rapid recovery of complete psychomotor function than thiopental. Methohexital, when compared to thiopental, produces more rapid return to consciousness, less tissue irritation and shorter periods of hypotension.[5,6] For these reasons, we chose methohexital anesthesia for cardioversion. The purpose of this study was to investigate and describe the use of methohexital anesthesia for cardioversion in a large group of patients with supraventricular dysrhythmias. Methohexital has not previously been reported as an anesthetic for cardioversion.

Methods-Informed consent and Institutional Review Board approval were obtained. 112 patients who were scheduled for cardioversion were studied. A subset of patients with rapid ventricular responses (RVR), baseline heart rates (HR) greater than 110 bpm, were further evaluated. Chronic medications were continued and no anesthetic premedication was given. Monitored variables included continous electrocardiogram (ECG), heart rate (HR), systolic blood pressure (SBP), response to respiratory rate, and verbal communication. Preoxygenation was followed by intravenous infusion of 10-20 mg. aliquots of 1% methohexital every 15-30 seconds until the patient no longer responded to verbal commands. Cardioversion was then attempted. Additional methohexital was given as necessary to maintain unresponsiveness in those patients requiring repeated countershocks. Maximum decrease in SBP and maximum increase in HR after induction were compared to baseline. Recorded data included the total drug dose and the cardioversion success rate. Complications examined included prolonged recovery time to verbal response (> 15 min.), dysrhythmias or hemodynamic instability requiring pharmacologic intervention, ischemic ECG changes, acute neurologic sequelae, recall, myoclonus, and burning on injection. Data are presented as mean ± SEM where appropriate. Data were compared to previous studies cited.

Results-The mean maximum decrease in SBP for all patients was 7.2% ± 0.9. Seven percent of the patients had a greater than 20% decrease in SBP. None of these changes required pharmacologic intervention. The mean maximum increase in heart rate for all patients was 4.1% ± 1.2. No patient with a baseline heart rate less than 100 bpm developed a heart rate greater than 110 BPM during the anesthetic.

Thirty two patients had baseline HR greater than 110 bpm with a mean HR of 130 ± 3 bpm for this subset. These patients with rapid ventricular responses (RVR) exhibited a mean maximum decrease in SBP of 6.7% ± 0.8. Only one of these 32 patients had a drop in SBP of greater than 20%. In the RVR subgroup, heart rate increased 1.2% ± 0.5. Of six RVR patients with baseline SBP less than 100 mmHg, none exhibited a drop in SBP greater than 20%.

	decrease in SBP mean ± SEM	increase in HR mean ± SEM	# patients with decrease SBP > 20%	success rate %
All Patients n = 1.2	7.2% ± 0.9	4.1% ± 1.2	8/112 (7%)	89
RVR subset n = 32	6.7% ± 0.8	1.2% ± 0.5	1/32 (3%)	94

The total drug dose was 1.23 mg/kg ± .1mg/kg. The cardioversion success rate was 89% overall, and 94% for patients with RVR. There was a 6% incidence of prolonged recovery, but all patients responded to verbal command within 30 min. Three patients had recall, two had burning on injection, and one had mild myoclonus. None of the patients developed ischemic ECG changes, dysrhythmias or hemodynamic instability which required intervention, or early neurological sequalae.

Discussion-Thiopental anesthesia for cardioversion has been shown to decrease SBP by 11% ± 1.2%. Six of 50 patients experienced greater than a 20% drop in SBP.[1] A similar mean decrease of 12% in SBP and a mean heart rate increase of 4% occurred in 15 patients anesthetized with propofol for cardioversion.[3] The success rate of cardioversion was 73%. Diazepam failed to produce amnesia in 32% of cardioversion patients,[1] and etomidate caused myoclonus in as many as 38% of patients anesthetized for cardioversion.[2] In our study, methohexital provided remarkable hemodynamic stability, amnesia, and cardioversion success, even in patients with uncontrolled heart rates and low preanesthetic blood pressures. We recommend methohexital anesthesia for DC cardioversion when administered in this manner. Clinical side effects were minimal, emergence was rapid, and the success rate was high compared to studies of other agents.

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TITLE: CENTRAL BLOCKADE OF INDUCED EMESIS BY A COMBINATION OF MORPHINE AND METHYLNALTREXONE IN THE DOG

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Introduction: Vomiting involves afferent stimuli from such diverse structures as the chemoreceptor trigger zone (CTZ) in the area postrema of the brain, the vestibular apparatus, and stretch and chemosensitive receptors in the gut and higher cortical function. Interpreting these stimuli and coordinating a response is a central function located in the medullary retching center and vomiting center, which are adjacent to the respiratory center and connected via the nucleus tractus solitarius. Emesis is then mediated through efferent voluntary and involuntary nervous pathways to the muscles of the gut, abdomen, and thorax.[1]

Morphine sulfate (MS) induces vomiting which can be blocked by the antagonist naloxone or ablation of the CTZ.[2] Methylnaltrexone (MNTX), an opioid antagonist with activity limited to the peripheral side of the blood-brain barrier (BBB), has recently been shown to block MS-induced vomiting, suggesting that the opioid emetic receptors of the CTZ are peripheral to the BBB.[3] MS has actions central to the BBB such as analgesia and sedation, and it has been suggested that central opioid receptors may inhibit emesis.[4]

In these experiments the effect of MS in combination with the peripheral opioid antagonist MNTX on vomiting induced by non-opioid emetic agents was studied to determine if MS had antiemetic activity at a site central to the BBB.

Methods: All protocols were approved by the Animal Care Committee. Male mongrel dogs (15-25 kg) were studied in two protocols using apomorphine (APO) and cis-platinum (CISP) as emetic agents.

Dogs were challenged with i.v. APO, 0.1 mg/kg (n=8) or 0.03 mg/kg (n=20), after being randomly assigned to receive no pretreatment, pretreatment with MNTX, 0.25 mg/kg, alone or MNTX, 0.25 mg/kg, plus MS, 1 mg/kg. After a 15 min period of acclimatization, animals were given the assigned pretreatment, and 30 min later they were given APO. Animals were observed for 60 min, or until recovered from the drug effects, for the number of emetic events (defined as expulsion of gastric contents), the time to the first event and level of sedation, which was subjectively scored on a four point scale (A=none, B=mild, C=moderate, D=unarousable).

Animals in the second protocol were challenged with CISP, 3 mg/kg i.v. These dogs were randomly assigned to receive either MNTX, 0.25 mg/kg, 30 min before and 60 min after the CISP infusion; or MNTX, 0.25 mg/kg, plus MS, 1.0 mg/kg, 30 min before and MNTX, 0.25 mg/kg, plus MS, 0.5 mg/kg, 60 min after the CISP infusion. Animals were observed for 5 hrs post challenge, and the animals' cages were examined the morning after the experiments for evidence of delayed emesis.

Results: APO without MS pretreatment reliably produced emesis in all groups. APO emesis was characterized by onset within 1-4 min with 2-6 emetic episodes (one animal had 15 emetic episodes). The emetic episodes were completed in 5-10 min. Animals without MS were all graded "A" on the sedation scale.

In each group the combination of MNTX and MS was effective in reducing emesis. With APO, 0.1 mg/kg, there was a 50% reduction in emesis. This did not reach statistical significance due to the small number of animals involved. In dogs given APO, 0.03 mg/kg, there was a highly significant 78% efficacy of MNTX and MS in preventing emesis. MNTX alone had no antiemetic effect against the 0.03 mg/kg dose of apomorphine. (Table 1)

Animals given MS all showed signs of sedation (scores B-C). No animals were scored as "D". No animal vomited after receiving MNTX plus MS. All animals recovered without apparent sequelae. There were no gross behavioral effects attributable to MNTX alone.

Table 1. Inhibition of apomorphine-induced emesis

Pre-Treatment	APO 0.03 mg/kg Animals With Emesis	APO 0.03 mg/kg Animals Without Emesis	APO 0.1 mg/kg Animals With Emesis	APO 0.1 mg/kg Animals Without Emesis
None	7 (100%)	0	4 (100%)	0
MNTX alone	4 (100%)	0	-	-
MNTX+ MS	2 (22%)*	7	2 (50%)	2

* $p < 0.01$ compared to no pretreatment

CISP with MNTX alone as pretreatment reliably produced emesis in all animals. CISP emesis was characterized by onset within 120-150 minutes with 11-18 emetic episodes (one animal had 4 emetic episodes). Animals without MS were all graded "A" on the sedation scale. No delayed emesis was observed.

Pretreatment with MNTX plus MS showed a 100% antiemetic effect. (Table 2)

Table 2. Inhibition of cis-platinum-induced emesis

Pre-Treatment	Cis-platinum 3.0 mg/kg Animals With Emesis	Cis-platinum 3.0 mg/kg Animals Without Emesis
MNTX alone	5(100%)	0
MNTX + MS	0 (0%)*	5

*$p < 0.01$

Animals given MS all showed signs of sedation (scores B-C). No animals were scored as "D". No animal vomited after receiving MNTX plus MS. There were no gross behavioral affects attributable to MNTX alone.

Discussion: MNTX in combination with MS was highly effective at blocking the emetic action of apomorphine, a DA-2 agonist known to act at the CTZ. The emetic action of APO is not blocked by opioid antagonists such as naloxone and was not blocked by MNTX in this study. MNTX antagonizes MS at sites peripheral to the BBB. We thus conclude that the emetic action of APO was being blocked by MS at a location central to the BBB when combined with the peripheral antagonist methylnaltrexone.

CISP-induced emesis has different characteristics than APO emesis, and while many agents show cross reactivity in blocking emetic effects, those agents with high activity against APO may have a low activity against CISP, and vice versa. This suggests that these agents are acting at different trigger points with common higher pathways. Naloxone,[5] and in this study MNTX, have no effect on the emetic action of CISP. MS in combination with MNTX was 100% effective in blocking CISP emesis, again indicating a central locus of action.

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(* Deceased May, 1989)

TITLE: TOTAL INTRAVENOUS ANESTHESIA WITH PROPOFOL ALFENTANIL, AND VECURONIUM FOR SUPERFICIAL SURGERY.

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Introduction. Propofol's pharmacokinetic profile makes it a useful hypnotic for continuous intravenous (IV) infusion. This study evaluated the feasibility and safety of a propofol (P)-alfentanil (A)-vecuronium (V) total intravenous anesthetic vs an alfentanil-nitrous oxide (N) technique which was simular to that described by Auseums et al.[1]

Methods. Twenty four healthy, ASA I-II patients, age 18-60, 40-90 kg, gave written informed consent to participate in this institutionally-approved study. They were randomly assigned to group I (N=12) who received IV: 1) P 2 mg/kg over 60 sec, then a 2-step continuous infusion designed to maintain a blood concentration of 2 ug/ml; 2) A 50 ug/kg/min x 3 min, then 50 ug/kg/hr with adjustments according to somatic or autonomic response or lack of response to surgical stimuli; and 3) V 0.06 mg/kg followed by an infusion to maintain an 80% or less neuromuscular block; or to group II (N=12) who differed from group I because they received 67% N instead of a P infusion. The IV drugs were delivered with an Omni-flow pump. A was stopped 15 min before and P and N were stopped 5 min before the end of surgery. Frequent arterial blood samples were obtained to measure P and A before, during, and after surgery expected to last 2 hours. A separate observer (D.P.) evaluated the speed and quality of recovery by noting the time to spontaneous eye opening (awake) and orientation to time and place; asking the patient to perform a Trieger and track tracer test before surgery and every 30 minutes after awakening until control values were achieved; and noting adverse effects in the perioperative period.

Results. Both groups were demographically similar. Hypotension and bradycardia occurred after induction of anesthesia in both groups. Blood pressure and heart rate returned toward control values after skin incision. P concentrations were generally within 10% of predicted and were a mean of 1.07 at awakening and 0.97 at orientation. A concentrations were variable. The A utilization was 144 ug/min in group I and 162 ug/min in group II. Awakening occurred in about 4.5 min after all anesthetics were discontinued in both groups but orientation to time and place was faster in group I. More patients in group I had Aldrete scores of 9 or 10 when they arrived in the recovery room. The recovery room period was remarkably free of side effects and the need for analgesic drugs.

Discussion. A total IV anesthetic with A, P and V was easy to administer with this technique and produced adequate anesthesia for superficial surgery with rapid, pleasant recovery. There were however, no great differences between the two techniques. The doses of both A and P used in this study initially produced hypotension and bradycardia and should be given in a different way in future studies.

Reference.

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TITLE: FLUMAZENIL REVERSAL OF MIDAZOLAM SEDATION IN THE ELDERLY

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Introduction. Midazolam (M) is used intravenously (IV) to sedate patients undergoing surgery under regional anesthesia. In the elderly M may have a more profound effect and longer duration of action than in younger patients. The specific benzodiazepine antagonist, flumazenil (F), could shorten the recovery period when M is used for IV sedation in elderly patients.

Methods: This study examined the safety and efficacy of flumazenil when used to reverse sedation of the elderly with midazolam. In a randomized, placebo-controlled, double-blind, institutionally-approved study, 30 patients, age 63 or older who were not taking interfering drugs, gave written informed consent and received IV either F (group 1, N=19) or placebo (group 2, N=11) in the recovery room to reverse M administered for sedation during regional anesthesia. F (0.1 mg/ml) or a placebo were initially given in 2 ml increments twice, a minute apart, and titrated in further 2 ml increments, if necessary, to reverse sedation until 10 ml was injected. Assessments by patient and observer of the degree of sedation, and observer assessed psychomotor tests and memory, were made before and periodically for 3 hours after the attempt to reverse M. Times for tests of mental function and psychomotor skills to return to control values were analyzed by the Mann-Whitney U test. A contingency table was used to analyze memory at each assessment time. P = <.05 showed significant group differences.

Results: The two groups were similar for age, weight, height, sex distribution, M dose and time of surgical procedure. There was no difference in the time patient-assessed sedation returned to control values. Two of three psychomotor tests and the observer's assessment of sedation returned to control values faster after F. Memory function was better after F for 15 minutes after attempted reversal but there were no group differences at 30 and 60 minutes. There was variability in the response to F, those receiving the most M were more likely to become resedated.

Discussion: Flumazenil, 0.4-0.6 mg, can rapidly reverse the sedative-hypnotic and amnestic effects of midazolam in elderly patients. However, the recovery of assessed functions were not maintained in all patients; resedation occurred in some of them. This is probably a function of the relative dose and timing of the agonist and the antagonist. When used in the manner described here, flumazenil has the potential problems of any short acting antogonist used to reverse the effects of a longer acting agonist.

TITLE: HEMODYNAMIC CONSEQUENCES OF DDAVP ADMINISTRATION AFTER PRIMARY CABG

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INTRODUCTION: The use of DDAVP to promote coagulation following cardiac surgery has increased. Initially thought to be devoid of hemodynamic sequelae, there is increasing evidence that administration of DDAVP can result in hypotension (1-2). This study was undertaken to evaluate the hemodynamic consequences of DDAVP given following primary CABG, and its impact on exposure to blood transfusion.

METHODS: Approval was granted by the University of Virginia Human Investigation Committee. After written informed consent, 40 patients undergoing primary CABG were recruited. Patients excluded were those receiving heparin or coumadin, or with coagulopathies. All operations were performed by the same attending surgeon. Anesthetic technique consisted of high dose narcotic with no inhalational agents used after CPB. Twenty patients were randomly assigned to receive DDAVP, 0.3 mcg/kg infused over 15 minutes, and twenty patients were given placebo. The OR team and data collector were blinded as to which solution was given. Protamine was administered immediately after removal of the aortic cannula and the study solution started 5 minutes later. Hemodynamic variables were recorded; prior to induction of anesthesia, prior to starting the study solution (time 0), then 5, 10, 15, and 30 minutes after start of the infusion. The quantity and nature of intravenous fluids administered during the DDAVP/placebo infusion was recorded. Inotropic support was initiated at the discretion of the OR team. Vasodilators were not administered unless systolic blood pressure exceeded 130 mmHg. Chest tube drainage was recorded for 24 hrs or until their removal.

A bleeding time, platelet count, PT, PTT, ACT, and HCT were obtained preoperatively, prior to starting the DDAVP/placebo infusion (except bleeding time), and in the ICU. Protamine dosage was calculated using a protamine titration technique.

The t-test and Chi^2 test were used for statistical analysis.

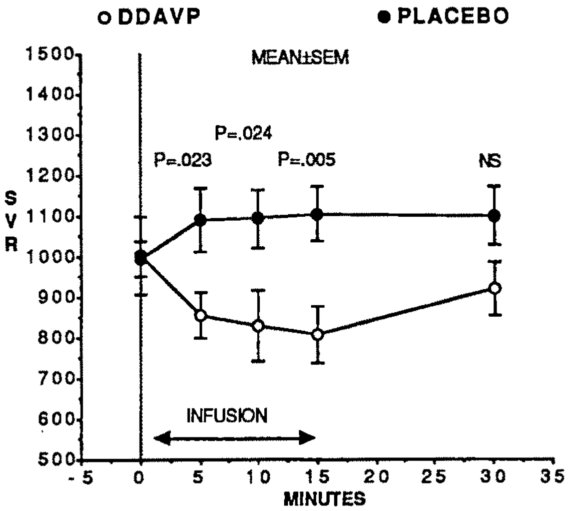
RESULTS: Preoperatively the study and control populations were comparable in regards to sex, age, BSA, preoperative drug regimes, and preoperative hemodynamics. In addition, the protamine dose, CPB time, use of inotropic support, and post-CPB use of vasodilators did not differ significantly.

A greater than 20% drop in the blood pressure (from time 0) measured at 5, 10, or 15 minutes was considered significant (Table 1). In three patients severe hypotension resulted in discontinuation of the study infusion. All three were in the DDAVP group.

TABLE 1	SYSTOLIC BP DROP		MEAN BP DROP		DIASTOLIC BP DROP	
	>20%	≤20%	>20%	≤20%	>20%	≤20%
DDAVP	9	11	5	15	5	15
PLACEBO	1	19	1	19	0	20
	p=.004		p=.077		p=.017	

DDAVP infusion resulted in a significant decrease in SVR (Fig.1) and increased cardiac output. The PA pressures, CVP, PCWP, and amount and nature of i.v. fluids administered did not differ significantly between the two groups.

FIGURE 1



There were no significant differences in coagulation parameters preoperatively, after protamine (prior to DDAVP), or postoperatively. The DDAVP group lost an average of 409 mls/M^2, while the placebo group lost an average of 363 mls/M^2. Transfusion of blood products is presented in Table 2.

TABLE 2	RBC	FFP	PLATELET	TOTAL	#PATIENTS
DDAVP	12	13	32	57	6 OF 20
PLACEBO	6	6	0	12	5 OF 20

DISCUSSION: This study examined the impact of DDAVP administration on hemodynamics and transfusion requirements for patients undergoing primary CABG. Our results show development of clinically significant hypotension in a large proportion of patients receiving DDAVP. This hypotension is a result of peripheral vasodilitation. In addition, DDAVP did not decrease blood loss, or reduce the need for blood transfusion. We conclude that DDAVP administration following primary CABG is associated with serious risk and unsubstantiated benefit.

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Title: ANESTHESIA FOR LITHOTRIPSY: EFFICACY OF MONITORED ANESTHESIA CARE WITH ALFENTANIL

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INTRODUCTION: Extracorporeal shock wave lithotripsy (ESWL) is now recommended for treating most renal calculi. Initial reports recommended general or major conduction anesthesia.[1,2] Newer generation machines are purportedly less painful and may be amenable to monitored anesthesia care (MAC). Our institution utilizes a second generation lithotripter, which lessens patient discomfort by delivering approximately 20% less power than the first generation machines and providing a wider area through which the shock waves enter the body (to a sharp focal point at the kidney). We present our retrospective experience with four anesthetic techniques in outpatients undergoing ESWL with a Dornier HM-4 nonimmersion model lithotripter, stationed in a mobile van.

METHODS: Following institutional Human Investigational Committee approval, charts of all outpatients who underwent ESWL from September 1988 to April 1989 were reviewed. The 141 patients were clustered into four groups based on anesthetic technique. (A)-General anesthesia consisted of intravenous thiopental induction with isoflurane and/or nitrous oxide maintenance. (B and C)-Both spinal and epidural anesthesia were accomplished with bupivacaine to approximately the fourth thoracic dermatome level. (D)-MAC consisted of pretreatment with intravenous midazolam (0.5-2 mg) and droperidol (0.625-1.25 mg) and maintenance with alfentanil first as a bolus (5 ug/kg) and then as a continuous infusion (0.25-0.5 ug/kg/min) with intermittent boluses as required. Data were analyzed with respect to: 1)total time in lithovan; 2)recovery time until discharge; 3)perioperative anesthetic complications. Times were analyzed with analysis of variance (ANOVA), utilizing Duncan's test for multiple comparisons. Complication rates were compared by chi-square analysis; $p<0.05$ was considered statistically significant.

RESULTS: Although there were no obvious differences in duration of surgical treatment, lithovan time was significantly shorter in the MAC group compared to the other three techniques. Recovery time also tended to be shorter in this group, resulting in a significantly shorter overall duration of combined lithovan plus recovery time for MAC patients. Alternatively, spinal anesthesia significantly prolonged recovery time compared to the other three groups (Table). Postoperative complications consisted exclusively of nausea, without significant difference among the groups.

DISCUSSION: Since its introduction for ESWL at our institution, MAC has become the technique of choice for lithotripsy (Figure). It has provided effective analgesia in the 67 cases in which it has been used, as alfentanil can be rapidly titrated to patient response. The technique has allowed for rapid turnover, both in the lithovan and recovery areas. The incidence of nausea has been low; this may be attributable to pretreatment with droperidol. Our experience with alfentanil, midazolam and droperidol is in contrast to that reported with fentanyl and midazolam; 12% of such patients could not complete the treatment under this regimen.[3] We conclude that MAC with alfentanil is the preferred anesthetic technique for ESWL using a newer generation lithotripter.

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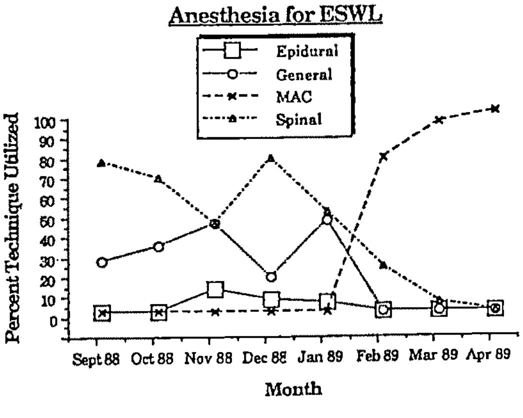
Technique	# of Cases	Litho Van Time (Min)	Recov. Time (Min)	Postop. Nausea
General	24	95±59	172±66	12.5%
Spinal	47	95±42	264±100	2%
Epidural	3	88±38	173±35	0
MAC	67	53±18	130±47	7.5%



Title: MORPHINE PLUS PROMETHAZINE FOR PATIENT CONTROLLED ANALGESIA

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INTRODUCTION: Administration of morphine by patient controlled analgesia (PCA) has improved postoperative analgesia, but often is associated with narcotic-related side effects including nausea, vomiting and pruritus.[1] Since phenothiazines traditionally have been added to IM morphine regimens, we decided to evaluate the feasibility and efficacy of combining small amounts of promethazine to our standard PCA dose of morphine.

METHODS: Following institutional Human Investigation Committee approval and informed written consent, 30 patients recovering from abdominal gynecologic surgery and requesting PCA in the postop period were randomized into 2 groups. Upon arrival on the ward, Group A (n=15) received morphine 1.5 mg with an 8 min. lockout; Group B (n=15) received a mixture of morphine 1.5 mg plus promethazine 0.5 mg with the same lockout. Complaints of nausea were immediately evaluated and treated by nurses blinded to the study drug. If indicated, the patient received droperidol 0.5 mg. If symptoms persisted a second dose was given; further symptoms were treated with transdermal scopolamine (TDS). In addition, patients were followed for 24 hrs by trained observers who recorded total drug dosages, the presence of pruritus, and the level of sedation. They also determined an objective nausea score, based on the following criteria: 0=no complaint of nausea; 1=mild nausea; 2=moderate nausea (treated with droperidol); 3=severe nausea (treated with droperidol); 4=nausea requiring treatment with both droperidol and TDS.

Data were analyzed by Wilcoxon-2 sample (non-parametric) test and Pearson Chi-Square analysis; $p<0.05$ was considered to be significant.

RESULTS: There were no differences noted in patient demographics, 24 hr narcotic requirements, pain, satisfaction, or sedation scores. The addition of promethazine to PCA morphine was well tolerated and produced no adverse side effects. Moreover, it decreased nausea and adjuvant antiemetic requirements. Nausea scores were significantly better for Group B ($p=0.03$). Only 27% of Group B patients required adjuvant antiemetic therapy, as opposed to 60% of Group A ($p=0.06$). Pruritus was reported by only 1 patient in Group A and by none in Group B.

DISCUSSION: We conclude that the addition of promethazine to morphine solutions for PCA is efficacious in decreasing nausea and the need for adjuvant antiemetic therapy. Such combination therapy may prove to be even more effective with larger doses of promethazine or the introduction of other agents. In many cases the safety and efficacy of narcotic/adjuvant combinations is already well established for other means of administration. In some settings, compatibility may first need to be established.

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	Group A	Group B
Median nausea score	2.5	0.0
Mean nausea score	2.13±1.67	0.86±1.46
% receiving drop	60	27
Total drop dose(mg)	0.47±0.2	0.19±0.2
% receiving TDS	33	13

TITLE: CARDIOVASCULAR CHANGES DURING ADENOSINE INDUCED HYPOTENSION FOR MAJOR ORTHOPEDIC AND CEREBRAL ANEURYSM SURGERY

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INTRODUCTION: Induction of an optimal hypotensive state to facilitate certain intracranial and orthopedic procedures requires an agent capable of producing a stable and predictable result with minimal adverse effects. The efficacy of Adenosine infusion was evaluated in patients undergoing controlled hypotension for cerebral aneurysm and total hip arthroplasty procedures.

METHODS: Six patients with informed consent to participate in this institutionally approved study, and free of pulmonary and cardiac disease underwent Adenosine induced hypotension for cerebral aneurysm (n=4) and total hip arthroplasty (n=2). Induction was achieved with IV injections of thiopental (4-5 mg/kg) and succinylcholine (1 mg/kg) prior to endotracheal intubation and controlled ventilation with Isoflurane 1%, N_2O 60% and O_2 40% for anesthesia. A quadruple lumen pulmonary artery catheter and radial artery cannula were inserted for monitoring of hemodynamic parameters and blood gas sampling. Adenosine (5.3 mg/mL in 5% mannitol) was administered into the right atrium by continuous infusion at a rate of 20 µg/kg/min initially, and increased at 20 µg/kg/min increments at 30 sec. intervals until the target mean arterial pressure (MAP) was reached. Target MAP for intracranial surgery was 40-50 mmHg, for total hip arthroplasty 55-65 mmHg. Hemodynamic parameters and arterial/mixed venous blood gas determinations were recorded prior to infusion, 30 min after a stable target MAP was achieved, and 30 min after termination of Adenosine infusion.

RESULTS: Adenosine infusion produced a dose dependent decrease in MAP to the desired levels with a mean titration period of 9.2±6.6 min. A very stable hypotensive state resulted requiring a maintenance dose of 77.3±34.9 µg/kg/min. Mean total dose was 388±141 mg for a mean duration of 72±41 min. A rapid, stable recovery was noted over a 5.5±4.9 min. recovery period. There was a 58% mean decrease in systemic vascular resistance index (SVRI) resulting in a mean 33% decrease in MAP. Cardiac index (CI) increased 30%, while the heart rate (HR) remained unchanged. Central venous pressure (CVP), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) all remained stable. There was a 38% decrease in pulmonary vascular resistance index (PVRI). Whole body O_2 delivery increased 20%, while O_2 consumption was unchanged. Effects of Adenosine on arterial and mixed venous blood gas tensions and pH values were minimal. A normal sinus cardiac rhythm was noted throughout the infusion and subsequent.

DISCUSSION: Adenosine infusion results in a smooth, rapid and predictable induction of a stable hypotensive state without tachyphylaxis and rebound effects commonly associated with other hypotensive agents. The reduction in MAP accompanies a profound decrease in SVR with enhanced CO and a stable HR. Cardiac filling pressures are maintained, implying little venodilation and suggesting that a preferential afterload reduction mediates the hypotensive effects of Adenosine infusion. Safety of the technique is supported by the enhanced total body O_2 delivery with an unchanging O_2 consumption. These findings suggest that Adenosine may prove to be a safe and effective means by which a hypotensive state may be achieved in order to facilitate certain surgical procedures.

Table 1 Systemic Hemodynamic Variables Before, During, and After Adenosine Infusion

	Before	During	After
MAP (mmHg)	75±11	50±7 ※	71±5
HR (beat/min)	94±7	96±6	89±3
MPAP (mmHg)	18±4	19±5	18±6
PCWP (mmHg)	11±3	11±3	9±5
CVP (mmHg)	10±3	10±4	7±5
CI ($l/min/m^2$)	3.6±0.8	4.7±1.1 ※	3.3±1.0
SI (ml/m^2)	40±9	48±10※	37±11
SVRI ($dyne \cdot sec/cm^5 \cdot m^2$)	1262±223	536±129 ※	1413±547
PVRI ($dyne \cdot sec/cm^6 \cdot m^2$)	172±96	107±79※	238±131

Mean±SD ※ $p<0.05$ vs Before

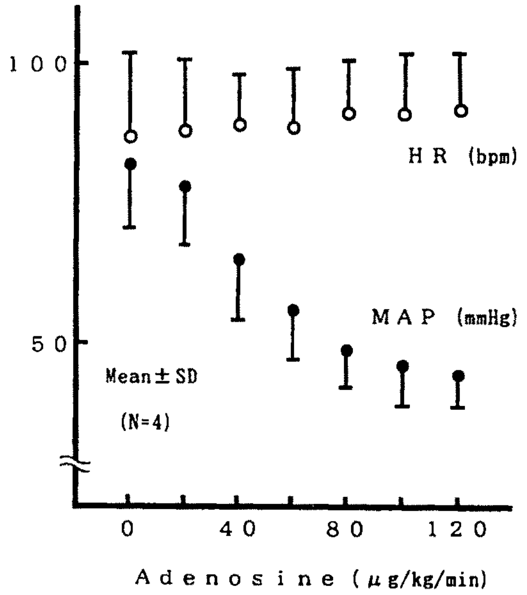

Figure 1

Title: THE EFFECT OF RESPIRATORY ACIDEMIA ON PULMONARY VASCULAR RESISTANCE FOLLOWING CARDIOPULMONARY BYPASS

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Introduction: Elevation of $PaCO_2$ in patients under general anesthesia has been reported to result in an increase in pulmonary vascular resistance (PVR).[1] Such response to hypercarbia could be particularly detrimental in the immediate post-cardiopulmonary bypass period when ventricular function may already be compromised.[2,3] To investigate this possibility, we prospectively examined the effect of hypercarbic acidemia upon PVR and right ventricular function in aortocoronary bypass patients immediately after weaning from cardiopulmonary bypass.

Methods: This study received institutional approval, and informed consent was obtained from each of the seven subjects studied. Only patients in normal sinus rhythm, hemodynamically stable and demonstrating normal clotting were considered acceptable for study. Any patient requiring post-bypass cardiac pacing, antiarrhythmic therapy, inotropic or vasoactive drips and/or inhalation anesthetics were excluded.

Upon termination of cardiopulmonary bypass and following heparin reversal, tidal volume was set at 10.28 ± .17 cc/kg, respiratory rate adjusted to establish a P_aCO_2 of 30 mm Hg (baseline), and FiO_2 adjusted to establish a PaO_2 greater than 150 mm Hg. Ventilatory settings were subsequently not altered during the study period. P_aCO_2 was increased from 30 (baseline) to 50mm Hg and then returned to 30mm Hg (finish) in stepwise fashion by addition and subtraction of 5% carbon dioxide to the breathing circuit. Patients were maintained a minimum of 10 minutes at each level of P_aCO_2 after which cardiac index (CI), central venous pressure (CVP), mean pulmonary artery pressure (PAP), left atrial pressure (LAP) and heart rate (HR) were measured. Differences in measured and derived parameters at all levels of P_aCO_2 were assessed by analysis of variance.

Results: No significant changes occurred in HR, CVP, LAP or CI as P_aCO_2 was increased from 30 (baseline) to 50 mm Hg (Table 1). However, significant increases did occur in PAP, PVR and RVSWI (Fig 1). As P_aCO_2 was subsequently lowered to 30 mm Hg (finish), PAP, PVR, and RVSWI declined significantly. At $PaCO_2$ of 30 mm Hg (finish), no significant change from 30 mm Hg (baseline) could be demonstrated for any of the measured or derived parameters.

Discussion: Respiratory acid-base status appears to have a profound influence upon the pulmonary vasculature immediately following cardiopulmonary bypass. Hypercarbic acidemia produces an increase in PVR, and consequently, RVSWI rises. Patients with poor right ventricular function may be unable to compensate for these hemodynamic changes and right ventricular failure can then ensue. Therefore, we conclude that respiratory acidemia in the immediate post-bypass period should be avoided.

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Table 1

MEASUREMENT	1	2	3
P_aCO2 (mm Hg)	29.9 ± 0.5	50.7 ± 0.9	30.8 ± 2.1
pH	7.47 ± 0.03	7.30 ± 0.03	7.47 ± 0.03
Rate (beats/min)	78.6 ± 12.2	77.7 ± 12.4	82.3 ± 13.0
PAP (mm Hg)	18.4 ± 3.4	21.9 ± 4.2**	18.4 ± 3.9
LAP (mm Hg)	9.1 ± 3.4	9.0 ± 3.4	9.4 ± 4.2
CVP (mm Hg)	9.9 ± 1.9	9.7 ± 1.6	8.7 ± 2.1
CI ($l/min/m^2$)	2.57 ± 0.90	2.47 ± 0.63	2.27 ± 0.53
PVR ($dynes/sec \cdot cm^{-5}$)	152 ± 37	213 ± 40**	160 ± 50
RVSWI ($gm\text{-}m/m^2/beat$)	3.6 ± 1.6	5.2 ± 1.3**	3.7 ± 1.3

mean ± SD, $^{**}p < 0.05$

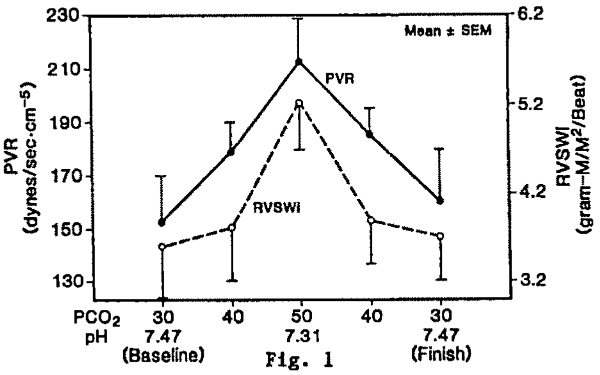

Fig. 1

Title: "IS MILRINONE AN EFFECTIVE INOTROPE DURING ISOFLURANE ANESTHESIA IN DOGS?"

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Introduction Milrinone is a new cardiac bipyridine, which has recently received FDA approval. Some important advantages of milrinone, as compared with amrinone are that it does not cause thrombocytopenia[1], it is more potent[2] and it is available in an oral preparation. Since there are no data regarding the efficacy of milrinone during isoflurane anesthesia, this study was undertaken to determine if milrinone is an effective inotrope in dogs with myocardial depression induced by beta-blockade and isoflurane anesthesia.

Methods This study was approved by the institutional animal care committee. Seventeen mongrel dogs weighing between 15-20 kg were pretreated with propranolol 80 mg. p.o. t.i.d. for 10 days and 2-3 mg IV on the day of the study. The dogs were anesthetized with thiamylal 3 mg/kg and anesthesia was maintained with isoflurane 1.6% end tidal concentration in 100% oxygen. Dogs were mechanically ventilated to maintain end tidal CO_2 between 32-34 mmHg. Catheters were inserted into the femoral artery and pulmonary artery via a femoral cutdown to measure systemic (BP) and pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO). A transducer tipped catheter (Millar #350) was passed retrograde into the left ventricle (LV) via a right carotid artery cutdown for direct LV pressure measurements and electronic derivation of LV dP/dt. BP, LV pressure and EKG were continuously recorded and systemic vascular resistance (SVR) was calculated using a standard formula. Maximum LV dP/dt was taken as the peak positive deflection of the LV trace. When hemodynamics were stable for at least twenty minutes, baseline measurements of the above variables were taken. Group one (control, N-7) received no milrinone. Group two (N - 10) then received a loading dose of milrinone,40 mcg/kg over one minute and then an infusion of 3 mcg/kg/min. Repeat measurements of hemodynamic variables were taken at 5, 15, 25 and 30 minutes in both groups. Intragroup and intergroup comparisons were made using mean changes from baseline and statistical analysis was performed using paired t-tests and ANOVA. Alpha (2-tailed was set at 0.05.)

Results (See Table) In the milrinone group the increase in Lv dP/dt max. was 130% compared with baseline ($p<0.001$) and it decreased 4% in the control group ($p>.05$). The comparison of change between groups was highly significant ($p<0.001$). There was a 31% increase in cardiac output compared to baseline in the milrinone group ($p<0.02$), while in the control group it increased only 3% ($p>.05$). The intergroup difference was significant ($p<0.05$). Pulmonary capillary wedge pressure was reduced 27% compared to baseline ($p<0.01$), in the milrinone group and in the control group it decreased only 6% ($p>.05$). The intergroup difference did not achieve statistical significance. Central venous pressure (CVP) fell by 28% in the milrinone group ($p>0.05$) and by 9% in the control group (($p>.05$). Heart rate increased 3% in the milrinone group ($p>.05$) and decreased 5% in the control group ($p<.04$). This difference between groups was statistically significant ($p<.005$). These peak changes all occurred within five minutes after the loading dose and remained constant for the duration of the study.

There were no statistically significant changes in MAP or SVR in either group.

Discussion The efficacy of this new inotrope during isoflurane administration is well demonstrated. Milrinone improved myocardial contractility as evidenced by increases in LV dP/dt and C.O. Since these variables were unchanged in the control group, it is clear that milrinone caused these hemodynamic alterations. In view of the fact that there were no significant changes in MAP and SVR and only a clinically insignificant change in HR, the increase in LV DP/dt was related to milrinone and not these other factors. This data suggests that milrinone is an effective inotrope in dogs with chronic beta blockade during isoflurane anesthesia.

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~~Table~~

CONTROL GROUP N=7

	--PRE INFUSION--		--POST INFUSION--		P-VALUE CHANGE WITHIN CONTROL	MILRINONE VERSUS CONTROL GROUP
	MEAN	SD	MEAN	SD		
MEAN BP	96.00	25.21	97.00	23.34		
CVP	4.14	2.34	3.96	2.85		
PCWP	8.00	3.21	7.68	3.86		
HR	108.14	7.08	102.79	10.01	0.040	0.005
CO	2.17	0.52	2.21	0.48		0.036
SVR	3579.41	1387.17	3517.26	1098.69		
DP/DT	1052.75	149.47	986.14	167.12		0.001

MILRINONE GROUP N=10

	--PRE INFUSION--		--POST INFUSION-		P-VALUE CHANGE WITHIN GROUP	MILRINONE VERSUS CONTROL GROUP
	MEAN	SD	MEAN	SD		
MEAN BP	89.60	14.83	98.23	18.29		
CVP	2.30	1.34	1.50	1.21		
PCWP	5.30	1.25	3.67	0.84	0.014	
HR	111.00	12.42	114.55	12.43	0.077	0.005
CO	2.51	0.52	3.18	0.70	0.014	0.036
SVR	2834.52	511.82	2573.34	730.26		
DP/DT	1359.01	244.31	3105.51	369.55	0.001	0.001

Title: LEUKOCYTE FUNCTION DURING AND AFTER CARDIOPULMONARY BYPASS

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Introduction:

Surprisingly little is known about the influence of cardiopulmonary bypass (CPB) on human leukocyte function, although recent reports have indicated that hypothermic CPB may be associated with impaired postoperative leukocyte function.Paradoxically,other studies of blood-membrane interactions(eg dialysis membranes)have found leukocyte activation. The aim of this study was to prospectively measure intra- and postoperative leukocyte number and function in cardiac surgery patients.Two important aspects of leukocyte function were assessed-aggregation and chemiluminescence. The latter is a measure of leukocyte free radical generation and thus an indirect assessment of bacteriocidal function.

Methods:

After institutional ethics committee approval,34 patients submitted for cardiac surgery were studied. 12 had coronary artery bypass surgery with hypothermic CPB(CPBH);12 had cryoablation of accessory conduction pathways during normothermic CPB (CPBN); and 10 patients had cryoablation of accessory conducting pathways without CPB(Cont). The latter patients served as the control group.

Blood samples were taken at four time periods- before CPB(T1), 30 minutes after starting CPB or a similar time in the control group(T2), at sternal closure(T3), and 24 hours post-operatively(T4). At each time blood was also sent for a white blood cell with differential count.For the leukocyte studies, anticoagulated whole blood was mixed with 6% dextran 500,000 in Hanks Balanced Salt Solution (HBSS ph 7.4). After 40 minutes incubation at room temperature the top layer was pipetted off and centrifuged.The red cells were lysed with cold distilled water and the final pellet of leukocytes resuspended in HBSS with 0.5% human albumen and cell viability of greater than 99% verified by Trypan blue exclusion. The cell concentration used was 10^7/ ml.

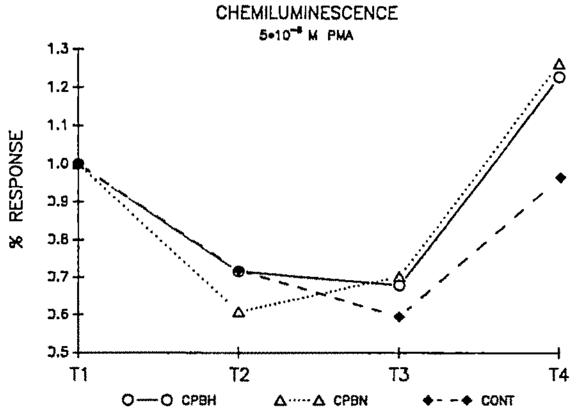
Aggregation and luminescence were measured simultaneously. The luminescence response to PMA which is a non-membrane dependent activator of protein kinase C and FMLP which stimulates a membrane receptor were assessed. Statistical analysis included ANOVA with Student-Newman-Keuls where appropriate

Results:

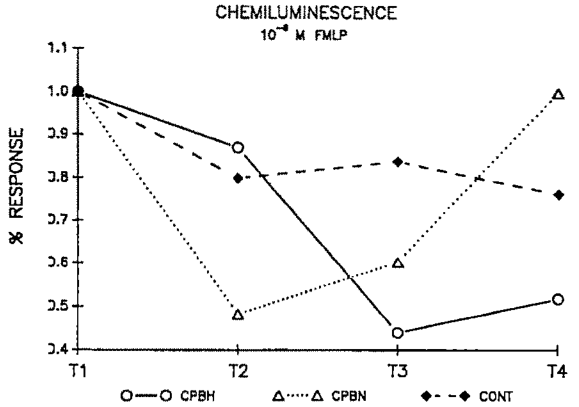
Leukocyte number decreased at T2 and increased above baseline at T3 and T4 in CPBH and CPBN. Cont showed a similar post surgical response.The aggregation and luminescence response to PMA was depressed in all 3 groups at T2 and T3 ($P<0.05$) but returned to baseline and in many to levels much above at T4(fig).Responses to FMLP were unchanged at all times in Cont. CPBH and CPBN showed a similar depression and rebound to that found with PMA(fig).

Discussion:

The depression in function found in the CPB groups suggests that extrapolation from studies of blood interactions with other synthetic membranes may not be appropriate.Similarly,changes in cell number as seen at T3 should not be equated with changes in cell function. The dramatic increase in cell function seen in some patients at T4 may reflect a rebound effect after depression or the emergence of a new cell population.The contribution of augmented leukocyte function to postoperative myocardial or pulmonary morbidity requires further prospective evaluation.The lack of change in FMLP stimulated function in the Cont group indicates that CPB but not anesthesia and surgery alone alters membrane receptor dependent and independent leukocyte functions.



CHEMILUMINESCENCE
$5 \cdot 10^{-8}$ M PMA



CHEMILUMINESCENCE
10^{-8} M FMLP

OXYGEN UPTAKE DURING CROSSCLAMPING OF THE THORACIC AORTA AND SODIUM NITROPRUSSIDE INFUSION IN DOGS

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Introduction: The study on 16 dogs examined the effects of controlled vasodilation on blood flows through the inferior and superior vena cavae as well as oxygen consumption above and below occlusion during crossclamping of the thoracic aorta.

Methods: Anesthesia was induced with sodium methohexital (8 mg·kg^{-1} i.v.) and then provided with halothane in oxygen titrated to maintain systemic arterial blood pressure within normal limits. End-tidal concentration of halothane was kept constant at 0.5%-0.8% during the experiments after surgical preparation was completed. Catheters were inserted into carotid and femoral arteries as well as into the superior vena cava, 3 cm from the atrium and into the inferior vena cava at the level of the diaphragm. A 5 F flow-directed thermodilution catheter was inserted into the pulmonary artery. Sternotomy was performed and after heparin administration, 300 u·kg^{-1}, the inferior vena cava was transected above the diaphragm and a cannulating electromagnetic probe of appropriate size was inserted. The animals were divided into 2 groups. In group 1 (8 dogs), the thoracic aorta was occluded for 30 min while in group 2 (8 dogs) the aorta was also occluded for 30 min but after 10 min of occlusion a sodium nitroprusside (SNP) infusion was initiated to decrease systemic blood pressure. Measurements were made at certain times before, during, and after aortic crossclamping. Hemodynamic variables were calculated according to standard formulae. Superior vena cava flow was calculated as a difference between cardiac output and inferior vena caval flow. Total body, upper and lower body oxygen consumption indices ($\dot{V}O_2I$, $UB\dot{V}O_2I$, $LB\dot{V}O_2I$, respectively), were calculated using the Fick equation. Animal care was in compliance with the Guide for Care and Use of Laboratory Animals published by the National Institute of Health.

Results: The main results of the study are presented in the table. During aortic crossclamping, total body oxygen consumption decreased in both groups. Oxygen uptake in the lower and upper parts of the body significantly decreased in both groups; this decrease in the lower part of the body was significantly more prominent during SNP administration than in the control group.

Discussion: The observed hemodynamic changes are in agreement with previous reports (1). SNP compared with control group increased cardiac index 1.5-2 fold. This increase was due to an increase in blood flow through the upper part of the body. The mechanisms for such an increase remains unclear (1). A more pronounced decrease in oxygen uptake below the aortic occlusion in group 2 than in group 1 was apparently due to a further decrease in blood flow since blood flow below aortic occlusion is pressure dependent (2). A substantial decrease in oxygen uptake in tissues above aortic crossclamping observed in both groups might result from quite a few different reasons including an increase in sympathoadrenal discharge which may constrict nutritive vessels thereby decreasing capillary density, oxygen delivery and uptake (3).

Conclusions: Crossclamping of the thoracic aorta at the diaphragmatic level was associated with a substantial decrease in blood flow and oxygen consumption in organs and tissues below aortic occlusion, and a substantial increase in blood flow, however with a decrease in oxygen uptake in the part of the body above the occlusion. SNP administered during aortic occlusion further increases cardiac output and blood flow through the upper part of the body, above aortic occlusion, and further decreases blood flow and oxygen consumption in the lower part of the body, below aortic occlusion. The latter is apparently due to a decrease in the distal aortic pressure. The mechanism of a decrease in oxygen consumption in the upper part of the body remains to be elucidated.

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Cardiovascular and Oxygen Consumption Data Observed During Crossclamping of the Thoracic Aorta (mean ± SE)

	Baseline	Crossclamping	Crossclamping + SNP
MAP			
I	78 ± 10	138 ± 12*	141 ± 15*
II	73 ± 6	138 ± 19*	100 ± 15* +
CI			
I	101 ± 23.7	120 ± 43.3	108 ± 46.0
II	119 ± 16.7	166 ± 60.4* +	198 ± 78.4* +
IVCFI			
I	48 ± 11.6	8 ± 2.4*	9 ± 2.9*
II	59 ± 8.1	10 ± 2.8*	9 ± 3.2*
SVCFI			
I	53 ± 13.9	112 ± 42.6*	99 ± 44.4*
II	61 ± 12.2	136 ± 58.0*	190 ± 78.5* +
$UB\dot{V}O_2I$			
I	3.5 ± 0.8	2.5 ± 1.0*	2.4 ± 1.0*
II	3.2 ± 0.74	1.8 ± 0*	2.0 ± 1.07*
$LB\dot{V}O_2I$			
I	3.2 ± 0.32	1.0 ± 0.28*	0.7 ± 0.33*
II	2.9 ± 0.5	0.9 ± 0.3*	1.0 ± 0.3* +

MAP = mean arterial pressure in mmHg; CI, IVCFI, and SVCFI = cardiac index, inferior vena cava flow index and superior vena cava flow index, respectively in ml·min^{-1}·kg^{-1}; $UB\dot{V}O_2I$, $LB\dot{V}O_2I$ = upper body oxygen uptake index and lower body oxygen uptake index, respectively in mlO_2·min^{-1}·kg^{-1}. Group I = control; Group II = sodium nitroprusside administration.
*$p<0.05$ vs baseline; + $p<0.05$ vs control at corresponding stage

TITLE: ADJUSTED DOSE INTRAOPERATIVE HEPARIN INFUSION DURING TOTAL HIP REPLACEMENTS UNDER EPIDURAL HYPOTENSIVE ANESTHESIA

AUTHORS: George Go, BS; Nigel E. Sharrock, MB, ChB; Robert Mineo, MS
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Introduction:

Fixed dose intraoperative heparin with a prolongation of activated partial thromboplastin time (aPTT) by 50% significantly reduced deep vein thrombosis (DVT) rate following total hip replacement (THR) from 24 to 8% when hypotensive epidural anesthesia was used.[1] Heparin is best administered in an adjusted dose regime as it is more effective and less apt to result in hemorrhagic complications. This study was undertaken to define an appropriate heparin dose regime for orthopedic surgery.

Methods:

After Institutional Review Board approval and patient consent, initial heparin doses of 1000 or 1500 units were given intravenously to two groups of patients as an initial bolus just prior to the start of THR surgery. Epidural catheters were inserted at least 1 hour prior to the initial heparin dose and hypotensive conditions were maintained throughout. Blood samples were drawn every 5 minutes for 30 minutes from arterial catheters to measure the activated clotting time (ACT) with the use of the Automated Coagulation Timer (HemoTec, Inc.). aPTT was also measured on the baseline, 5, and 30 minute samples using the same timer. In addition, 16 patients received infusions of heparin at a mean rate of 1200 units per hour initiated immediately after the initial heparin bolus dose.

Results:

The mean and S.D. of the ACT following 1000 and 1500 unit boluses of heparin are shown in figure 1. Both prolonged ACT by >30% at 5 and 10 minutes but the ACT declined with time so that at 30 minutes it was similar to baseline value in both groups. Patients receiving a constant heparin infusion are shown in figure 2. A correlation between ACT and aPTT is shown in figure 3.

Discussion:

Both 1000 and 1500 unit boluses of heparin are reasonable initial doses, providing increases in ACT of 35 and 50% respectively. A constant infusion seems to provide a more consistent anticoagulation response. ACT correlates well with aPTT at the low heparin dose and is therefore a convenient method of adjusting heparin dose intraoperatively. Monitoring of coagulation time is recommended as individual patient responses to intravenous heparin varies. This enables the heparin dose to be adjusted to response.

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Figure 1

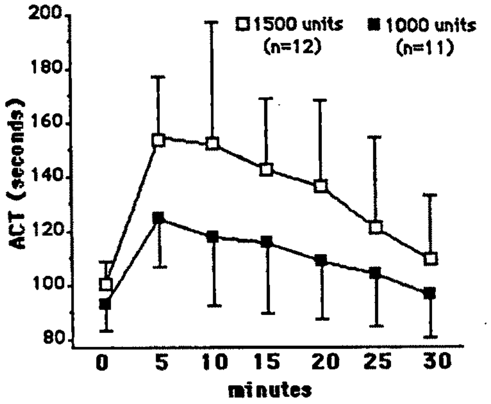


Figure 2

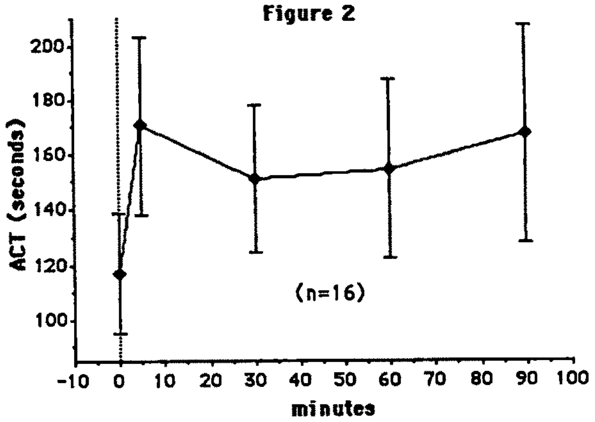
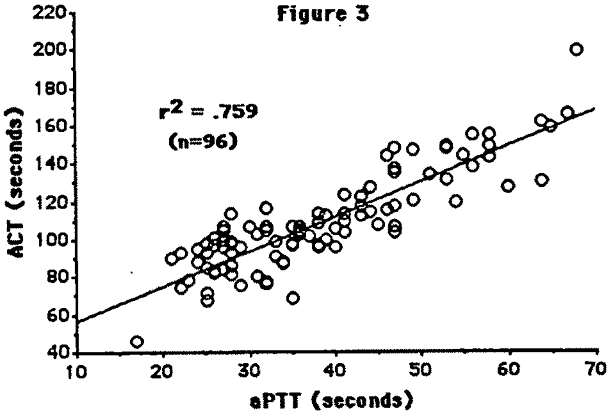


Figure 3



Title: HIGH-DOSE NALOXONE DURING CPR IN A PIG MODEL DOES NOT IMPROVE CEREBRAL OR MYOCARDIAL BLOOD FLOW

Authors: H.W.Gervais, M.D., B.W.Eberle, M.D., H.J.Hennes, M.D., D.Konietzke, M.D., W.Grimm, Ph.D.*, A.Kilian, M.D., C.Massing, M.D., W.Dick, M.D.
Affiliation: Departments of Anesthesiology and Nuclear Medicine*, Johannes Gutenberg University, D-6500 Mainz, FRG

Introduction. Naloxone (N) has been shown to improve hemodynamics and survival in hemorrhagic (1), endotoxic (2), and spinal shock (3). In man N temporarily abolished neurologic deficits after focal cerebral ischemia (4). In dogs N reduced the incidence of arrhythmias and ventricular fibrillation (VF) during myocardial ischemia by coronary artery ligation (5). Moreover, N has been shown to be of potential benefit in improving cardiac rhythm in post countershock electro-mechanical dissociation (EMD) (6).The aim of our study was to determine the effects of a single high-dose N bolus injection during closed-chest CPR after prolonged global ischemia on cerebral (CBF) and myocardial (MBF) blood flow.

Methods. After approval by the State Animal Investigation Committee, 21 pigs (18.2 ± 1 kg BW) were anesthetized with i.v. metomidate, intubated with a cuffed endotracheal tube and mechanically ventilated with N_2O/O_2 ($PaCO_2 \sim 35$ mm Hg). Pancuronium i.v. was given as needed. Saline-filled catheters were advanced through two femoral arteries and one femoral vein into the abdominal aorta (2 catheters: one for microsphere withdrawl and one for pressure measurement), left ventricle, and right atrium, respectively. Mean vascular pressures were measured in the right atrium (RA) and the abdominal aorta (AO). CBF and MBF (ml/min/100 g) was determined by injection of radiolabeled microspheres (15 ± 3 µm diameter) into the left ventricle. VF was induced by transthoracic AC shock, and ventilation was stopped. After five minutes of ischemia, conventional closed-chest CPR was commenced using a pneumatic chest compressor (Thumper®, Michigan Instruments) positioned over the lower two thirds of the sternum set to 60 compressions/minute, 50 % duty cycle, and a compression/ventilation ratio of 5 : 1 ($FiO_2 \geq 0.8$). The force of the compressor was set to produce a cyclic sternal displacement of approximately 20 % of the antero-posterior chest diameter. Immediately after commencing CPR, epinephrine 40 µg/kg was given i.v. followed by a continous infusion of 0.4 µg/kg/min. After 5 min of CPR, 11 animals received N 10 mg/kg iv (N concentrate containing 5 mg/ml); a control group of 10 animals received an equal volume of normal saline. RA, AO, CBF, and MBF were assessed before induction of VF and after 1, 15, and 30 min of CPR. After 35 minutes of CPR, the chest compressor was turned off, ending the experiment.

Results. RA, AO, and CPP were not different between groups before and during CPR; only after 30 min of CPR, AO in the N treated animals was significantly higher (26 ± 4 vs. 13 ± 3 mm Hg). After 1 min of CPR, CBF and MBF fell to 50 % and ~ 10 % of the pre-arrest values, respectively, further declining rapidly thereafter without differences between N and saline treated animals.

Discussion. In this animal model of prolonged closed-chest CPR after 5 min of ischemia, N 10 mg/kg had no clinically useful effect on RA, AO, CBF, and MBF. N when given during CPR did not improve hemodynamics or vital organ blood flow. Circulatory improvements observed with N during post defibrillation EMD or other shock states may require an organized electrical rhythm to exert positive effects on global and regional circulation. Since we did not attempt to defibrillate the animals, we cannot draw conclusions about survival after restoration of spontaneous cardiac activity. We conclude that in contrast to various shock states and models of cerebral ischemia, endogenous opiates may not be of importance during cardiac arrest and artificially maintained circulation by CPR.

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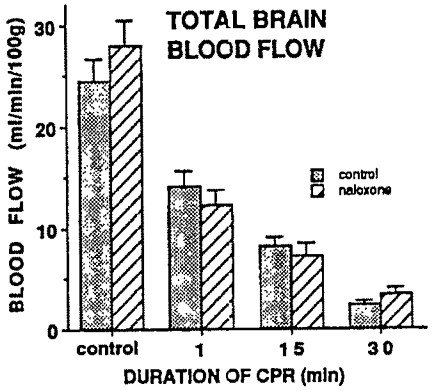

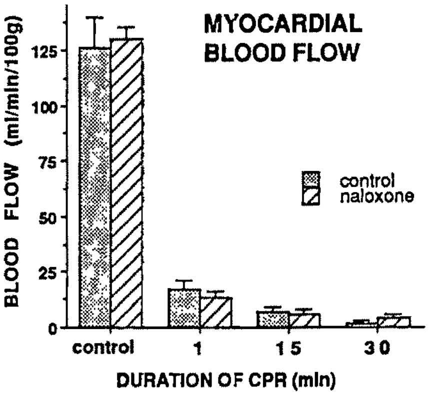

Title: **COMBINING ATRACURIUM AND VECURONIUM PROLONGS THE DURATION BUT DOES NOT REDUCE THE ONSET TIME OF NEUROMUSCULAR BLOCKADE IN MAN**

Authors: N. M. Gibbs, MBBS, FFARACS, G. W. Rung, M.D., P. W. Braunegg M.D., D. E. Martin, M.D.

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INTRODUCTION: Several investigators have demonstrated synergism between the neuromuscular blocking properties of atracurium (ATR) and vecuronium (VEC), both *in vivo*[1,2] and *in vitro*[3]. However, due to the conflicting results of previous studies, it has not been clear to what extent this synergism affects the onset time and the duration of neuromuscular blockade in man. The aim of the present study was to compare the onset time and the duration of neuromuscular blockade produced by atracurium and vecuronium in combination, with that produced by either drug alone, in a randomized, double blind, clinical trial.

METHODS: After institutional clinical investigation committee approval and written informed consent, 30 adult ASA class I or II patients undergoing general anesthesia for elective surgery were studied. Patients with neuromuscular disease, a risk of esophageal reflux, or greater than 20% above ideal body weight were excluded. All patients required tracheal intubation. Patients were randomized into five groups. Group 1 received ATR 0.6mg.kg^{-1}, Group 2 VEC 0.1mg.kg^{-1}, Group 3 ATR 0.15mg.kg^{-1} + VEC 0.025mg.kg^{-1}, Group 4 ATR 0.3mg.kg^{-1} + VEC 0.05mg.kg^{-1}, and Group 5 ATR 0.6mg.kg^{-1} + VEC 0.1mg.kg^{-1}. Neither the investigators, nor the anesthesiologists involved in the care of the patients, were aware of the group to which each patient had been assigned. The anesthetic technique was similar in all groups. Anesthesia was induced with fentanyl 1-2mcg.kg^{-1} i.v. and thiopental 4-5mg.kg^{-1} i.v. The study muscle relaxant was then administered over 15s. Anesthesia was maintained with 66% N_2O in oxygen. Supplemental doses of fentanyl were given as required. No volatile agents were used. Neuromuscular blockade was assessed by measuring the depression of the single twitch (T_1) of the Abductor Digiti Minimi, using a Puritan-Bennett Electromyographic Neuromuscular Transmission monitor. The control twitch (T_C) was obtained after induction, but before the administration of the study muscle relaxant. The onset time was taken as the time to 90% reduction of twitch height (T_1/T_C=10%). The duration was taken as the time to 10% recovery (T_1/T_C=10%). The onset times and durations produced by the combinations of the two drugs were compared to the corresponding times produced by either drug alone, using multiple one-tailed Student's 't' tests. Because multiple simultaneous comparisons were used, only P values <0.01 were considered significant.

RESULTS: There was no significant difference in either the mean age or the mean weight between the five groups. The onset times are displayed in figure 1. Only full-dose combinations of ATR + VEC produced a significantly shorter onset time. Half-dose combinations produced a slight reduction in onset time (12%), but this was not significant. The durations are displayed in Figure 2. Half-dose combinations produced a 40% (*vs* ATR) and a 25% (*vs* VEC) increase in duration. Similarly, full dose combinations produced an 85% (*vs* ATR) and a 60% (*vs* VEC) increase in duration. P values are given on the figures.

DISCUSSION: To our knowledge, this study is the first randomized, double blind assessment of the effects of ATR + VEC combinations on the onset *and* duration of neuromuscular blockade in man. Our results demonstrate that combinations of ATR + VEC prolong the duration of neuromuscular blockade. As such, our results support the findings of previous studies which have demonstrated synergism between ATR and VEC[1,2,3]. However, we found that half-dose ATR + VEC combinations did not result in a significant reduction in onset time. This finding does not discount synergism, but rather supports the concept that the distribution phase of non-depolarizing muscle relaxants is the *rate-limiting step* in the onset of non-depolarizing neuromuscular blockade[4]. All anesthesiologists should be aware of the prolongation of neuromuscular blockade if ATR and VEC are used during the same anesthetic.

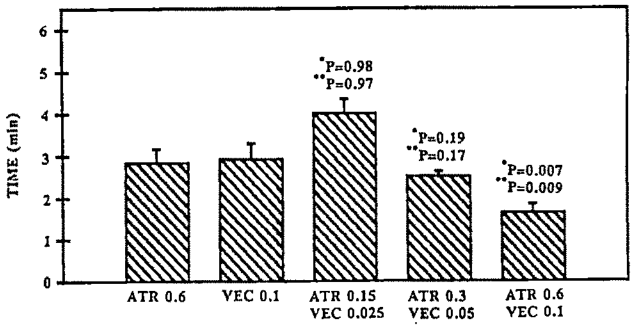

Figure 1. Onset of neuromuscular blockade (time to T_1/T_C=10%). Bars indicate mean±sem. (*vs* ATR, ***vs* VEC).

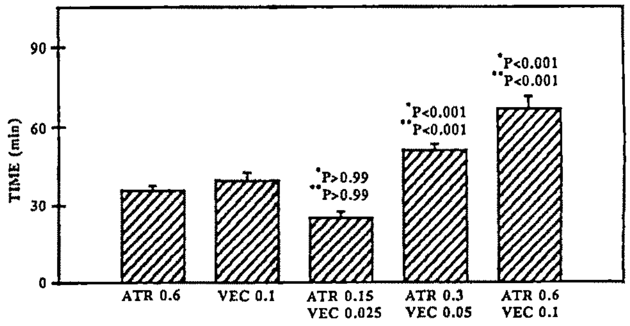

Figure 2. Duration of Neuromuscular blockade (time to recovery to T_1/T_C=10%). Bars indicate mean±sem. (*vs* ATR, ***vs* VEC).

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Title: LACTIC ACIDOSIS REDUCES INJURY OF MOUSE CORTICAL NEURONS DUE TO OXYGEN-GLUCOSE DEPRIVATION IN VITRO

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Introduction: Ischemic brain injury is associated with the development of lactic acidosis. Higher pre-ischemic blood glucose levels have been correlated with more severe lactic acidosis and greater neurologic or histologic deficit[1,2]. Despite this, the precise effects of lactic acidosis on neuronal injury *in vivo* are not well understood. Indeed the suggestion has been made that lactic acidosis may not necessarily be injurious to neurons since hippocampal slices subjected to hypoxia with added lactic acid were found to recover neuronal function better than control slices[3], and in the setting of hypoglycemia lactate was demonstrated to restore neuronal function[4]. Additional grounds to question the deleterious effects of lactic acidosis on neuronal tolerance to hypoxia or ischemia comes from two other findings. First the observation that moderate acidity decreased N-methyl-D-aspartate (NMDA) induced currents in hippocampal neurons[5]; the activation of these receptors is thought to contribute to the pathogenesis of ischemic neuronal injury[6]. Second the finding that moderate acidity in fact reduced the vulnerability of cultured neocortical[7] or hippocampal (Tombaugh and Sapolsky, personal communication) neurons to injury by combined oxygen and glucose depletion. The present study was carried out to determine whether the concurrent presence of pathophysiologically relevant concentrations of lactate altered this protective effect of H^+ *in vitro*.

Methods: Primary cortical cell cultures were prepared from fetal mice (day 15-17 gestation) generally as previously described[8]. Glial replication was inhibited with 10^{-5}M cytosine arabinoside at day 9-11 in culture. Ischemic exposure was initiated by washing cultures free of growth medium and into a defined salt solution lacking both glucose and oxygen (previously equilibrated with anoxic gas). After 45-60 min in an anoxic incubator at 37°, glucose and oxygen were reintroduced and the cells were returned to a normoxic incubator overnight to allow full expression of delayed neuronal death. Resultant neuronal cell death was assessed by phase contrast microscopy and by assaying the bathing medium for released lactate dehydrogenase, the release of this enzyme linearly correlates with the number of neurons that die by light microscopic criteria[9]. All experimental animal handling and care was in accordance with the requirements of our institutional Animal Investigation Committee.

Results: Within 24 hr after 45-60 min of combined oxygen and glucose deprivation at pH 7.4, the majority of cortical neurons degenerate and release lactate dehydrogenase to the bathing medium. The glia remain morphologically intact and cultures of glia remain morphologically intact and cultures of glia alone release essentially no lactate dehydrogenase under these conditions. However sister cultures exposed to ischemia in the presence of 40 - 60 mM DL-lactate (20 - 30 mM L-lactate) at pH 6.0 showed markedly less neuronal injury. A similar neuroprotective effect was seen in other sister cultures exposed to ischemia at pH 6.0 without added lactate.

Discussion: These experiments suggest that lactic acidosis can protect cortical neurons from damage induced by oxygen and glucose deprivation. The level of L-lactate studied here, 20 - 30 mM, is comparable to that reached in ischemic brain after elevation of blood glucose[2]. The neuroprotective effect of lactic acidosis appears to be largely an effect of lowered pH, as lowering pH alone without lactate was similarly protective. While further studies will be needed to establish the precise mechanism of this neuroprotective effect, down-modulation of NMDA receptor activation by H^+ seems plausible. It may be that the worsening of brain injury associated with acidosis in animal models of ischemic reflects the effects of H^+ on elements other than neurons, e.g. glia or vascular elements.

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TITLE: EVALUATION, IN DOGS, OF A SODIUM NITROPRUSSIDE CLOSED-LOOP DELIVERY DEVICE FOR HYPOTENSIVE ANESTHESIA

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INTRODUCTION:

A closed-loop delivery device for sodium nitroprusside (SNP) is commercially available for control of blood pressure after cardiovascular surgery (Titrator™ MODEL 10K, IVAC Corp). This device automatically regulates the infusion of SNP to maintain a desired blood pressure by implementing an adaptive proportional-integral-derivative control algorithm similar to that of Sheppard [1] and Slate [2]. In a study of 180 cardiac surgery patients, mean arterial pressure (MAP) was maintained within ± 10% of the target MAP 85% of the time during automated control compared to 61% with manual control [3]. The Titrator performed as well as experienced anesthesiologists in lowering and maintaining MAP 30 mmHg below baseline in dogs [4]. This study was conducted to evaluate the Titrator's ability to induce and maintain deliberate hypotension while subjected to various challenges to blood pressure homeostasis. The study was approved by the Institutional Animal Use Review Committee.

METHODS:

Anesthesia was induced in ten mongrel dogs (15-30 kg) with sodium thiopental 20 mg/kg, and maintained with halothane, 50% nitrous oxide and oxygen. Desired MAP (setpoint) was kept constant at 50 mmHg throughout the study.

The "time to setpoint" mode was tested 3 times in each dog by lowering the MAP to 50 mmHg over a period of 30 mins, over 15 mins and in the "off" mode in a randomized order. When in the "off" mode, the desired MAP is reached as quickly as possible. The controller's stability was evaluated by administering four challenges in randomized order: a 10-min infusion of isoproterenol (1.0 mcg/kg/min), a 10-min infusion of norepinephrine (0.25 mcg/kg/min), an isoproterenol bolus (0.5 mcg/kg), and a norepinephrine bolus (0.5 mcg/kg). A 15 minute recovery period was included after each challenge. To evaluate the controller's response to severe blood loss, 15 ml/kg of blood was withdrawn from the femoral artery over 5 min. After 20 minutes, the blood was reinfused to simulate intra-operative blood administration. To evaluate the controller's ability to return MAP to baseline after hypotension has been maintained, pressure was returned to 80% of baseline MAP at a controlled rate of 15 minutes in five dogs, and 30 minutes in five dogs.

RESULTS:

The desired MAP (± 10%) was achieved after 28.1 ± 3.9 min (mean ± SD), 17.2 ± 5.2 min, and 9.3 ± 3.9 min when the "time to setpoint" was set at 30 min, 15 min and "off" respectively. The average decrease in MAP for the three time periods was 45 ± 13 mmHg, 45 + 11 mmHg, and 41 ± 15 mmHg respectively. During the 10 minute period after setpoint was reached, MAP was maintained within ± 10% of the setpoint 86 ± 17% of the time for the 30 min "time to setpoint", 89 ± 13% for the 15 min, and 82 + 27% when "off. The maximum deviation from setpoint caused by each drug challenge, settling time (time required for MAP to return to ± 10% setpoint), and controller overshoot are displayed in Table 1. Blood loss caused a 12.0 + 3.7 mmHg decrease in MAP; blood replacement increased MAP 13.3 ± 4 mmHg. At the end of the study, MAP was returned to 80% of baseline after 13.9 + 3.4 min when set at 15 mins and 25.3 + 3.8 min when set at 30 min.

	Max Deviation (mmHg)	Settling Time (min)	Controller Overshoot (mmHg)
Iso Bolus	15 ± 5.8	5.3 ± 3.4	9.2 + 3.5
Iso Inf On	21 ± 4.7	4.7 ± 1.2	6.7 ± 5.1
Iso Inf Off	20 ± 4.1	8.3 ± 3.0	0.7 ± 1.2
Nor Bolus	27 ± 9.9	2.0 ± 1.6	5.4 ± 3.1
Nor Inf On	26 ± 13.1	6.0 ± 0.6	0.0
Nor Inf Off	10 ± 3.3	7.0 ± 1.4	4.1 ± 2.9

DISCUSSION:

During the induction of deliberate hypotension, a smooth transition to the setpoint was achieved and the desired pressure was maintained with a clinically acceptable degree of accuracy. After the bolus injection of isoproterenol and norepinephrine, the controller reacted properly by monitoring MAP to determine if the response was transient. This allows for only a slight increase or decrease of the infusion rate to prevent over-shooting of the setpoint. The continuous infusion of isoproterenol posed the greatest challenge; however, the controller reacted appropriately by discontinuing the SNP infusion approximately one minute after the hypotensive effect occurred. After discontinuation of the infusion, setpoint was re-attained with minimal overshot. Upon initiation and discontinuation of the norepinephrine infusion, the controller was able to re-attain the setpoint with minimal overshoot. The Titrator returned the MAP to baseline in a controlled manner, without evidence of rebound tachycardia or hypertension that is commonly observed after deliberate hypotension with SNP.

Controlling blood pressure with SNP can be a time consuming task required of the anesthesiologist due to the need for frequent infusion rate adjustments. An automatic controller can maintain deliberate hypotension and give the anesthetist more time for patient care. The results of this study demonstrate this device adequately responds to challenges to blood pressure homeostasis, and may be useful for automatically controlling the induction and maintenance of deliberate hypotensive anesthesia with SNP.

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TITLE: OPIOID RECEPTOR MEDIATED EFFECTS OF MEPERIDINE IN RAT SKELETAL MUSCLE.
AUTHORS: B. Glosten, M.D., S. Glusman, M.D., Ph.D.
AFFILIATION: The Department of Anesthesia, The University of Chicago, Chicago Il 60637

INTRODUCTION: By interacting with different opioid receptors, opioid agonists produce various effects. Meperidine, a mu receptor agonist, has some unique properties for a narcotic: it has local anesthetic effects, and it abolishes shivering better than other narcotics.[1] We studied the effects of four narcotics on skeletal muscle function to determine whether a peripheral action plays a role in these effects. We used the rat diaphragm as an example of a skeletal muscle composed of both "fast" and "slow" fibers, the extensor digitorum longus (a "fast" muscle), and the soleus (a "slow" muscle).

METHODS: After institutional approval from the animal research committee, Sprague Dawley rats were anesthetized with ether and a segment of diaphragm, extensor digitorum longus, or soleus muscle was removed. The muscle was fixed to the floor of a perfusion chamber and the tendon attached to a force transducer. The preparation was perfused with modified Ringers solution containing curare and aerated with 95% O_2, 5% CO_2. A tension of 10 grams was applied to the muscle. The muscle was supramaximally stimulated with bipolar field electrodes at 0.1Hz. Different concentrations of meperidine, morphine, fentanyl, and sufentanil were added to the perfusate and the effects on twitch tension were recorded.

RESULTS: Meperidine, $1X10^{-3}M$ caused a significant and reproducible augmentation of muscle twitch tension (16-172%) followed by complete suppression of the twitch (Fig 1A) in the diaphragm preparation. The augmentation, but not the suppression, was blocked by naloxone, $5X10^{-4}M$ (Fig 1B). Morphine, fentanyl, and sufentanil caused insignificant (0-6%) increases and no depression in twitch tension at concentrations up to 10 times more potent (clinically) than meperidine. Meperidine had similar effects on the pure "fast" muscle, the extensor digitorum longus muscle, (augmentation of twitch followed by suppression), but caused only twitch suppression in the pure "slow" muscle, the soleus muscle.

DISCUSSION: Meperidine has a dual action in the diaphragm and extensor digitorum muscle preparations: 1) a potentiation of twitch tension that is mediated by opioid receptors (blocked by naloxone), and 2) complete twitch depression that is not opioid receptor-mediated, an action that probably corresponds to the local anesthetic effect of the drug. That the opioid-receptor mediated augmentation is seen only with meperidine and not other mu agonists suggests that this action of meperidine may be mediated by a different opioid receptor or receptor subtype. The diaphragm is composed of both "fast" and "slow" muscle fibers. The dual effect of meperidine appears to be specific to "fast" muscle fibers as it occurs in the extensor digitorum longus (a "fast" muscle) and not in the soleus muscle (a"slow" muscle).

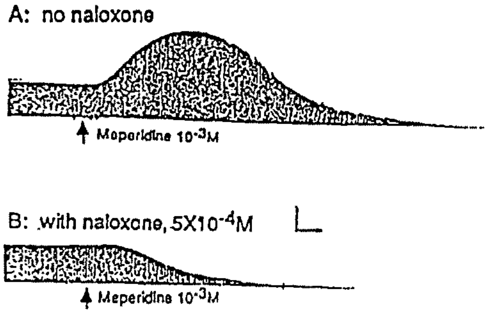
A: no naloxone
B: with naloxone, $5X10^{-4}M$

Fig 1. Cal: 2 g, 200 msec. A. Meperidine potentiates, then blocks, twitch tension in the diaphragm preparation. B. Naloxone prevents the potentiation of twitch tension by meperidine.

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Title:
CANINE END-SYSTOLIC PRESSURE-LENGTH RELATIONSHIPS: DEPRESSED BY DILTIAZEM, INVALIDATED BY ISCHAEMIA.

Authors: A.H.Goldberg, MD, PhD, J.Diedericks, FFA(SA), MMed, P.Foëx, DM, DPhil, FFARCS, & W.A. Ryder.
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Introduction: The end-systolic pressure-volume relationship is recognized as the most sensitive and specific index of myocardial contractility in the intact heart (1). As volume is difficult to measure, end-systolic pressure-length relationships have been considered useful substitutes. Whether they can be used to characterize contractility in the face of regional ischaemia has not been elucidated. This study was designed to determine whether the end-systolic pressure-length relationship (ESPLR) reflects changes in regional contractility during the imposition of graded ischaemia, and whether it is modified by diltiazem during propofol anaesthesia.

Methods Studies were conducted according to the Animals (Scientific Procedures) Act (1986) of the U.K. Seven Beagles were premedicated with morphine (1 mg/kg i.m.), induced with thiopental, and anesthetized and ventilated with halothane (0.7-1.5% in O_2/N_2). The heart was exposed through a left thoracotomy; a micrometer-controlled snare and a flow probe were placed around the left anterior descending coronary artery (LAD). Another flow probe was placed around the root of the ascending aorta. Left ventricular (LV) subendocardial length in the region of the LAD were measured by sonomicrometry. LV pressure was recorded from a cannula inserted through the apical dimple. An occluder around the descending thoracic aorta was used to increase afterload. After completion of the surgical preparation, halothane was replaced by propofol (5 mg/kg bolus followed by 200 mcg/kg/min infusion). Following recording of control data (C), LAD flow was gradually reduced to obtain: critical constriction (CC, decreased coronary flow pulsatility with no discernible deterioration in wall motion); Ischaemia 1 (I1, onset of post-systolic shortening (PSS)); Ischaemia 2 (I2, PSS plus systolic bulging); and total occlusion (TO). At each stage, afterload was increased by partial occlusion of the descending thoracic aorta for 5-8 cardiac cycles. Simultaneous measurements of LV end-systolic pressure and apical muscle length were used to obtain ESPLR slopes and X-axis intercepts (L0). The same protocol was repeated after i.v. diltiazem (D, 150 mcg/kg). Data were analysed by two-way ANOVA with Duncan's test for separations, and paired t-tests.

Results: The slope of the ESPLR was reduced by D at all stages but I1. Critical coronary constriction, I1 and I2 did not modify the ESPLR slope. However, TO caused a large increase in the slope. L0 was unchanged by D except at CC. Ischaemia 2 and TO led to significant increases in L0, indicative of a shift to the right of the ESPLR. (Figure 1.)

Discussion: While negative inotropic interventions in the presence of normal blood flow depress the ESPLR slope, as seen after D, ischaemia shifts the relationship towards larger length intercepts. Complete coronary occlusion (TO) was also associated with a paradoxical increase in the ESPLR slope. In the absence of ischaemia, the ESPLR may be a valid measure of myocardial contractility. However, in the face of severe regional ischaemia, accompanied by segmental dilation, the ESPLR is determined by the function of the normal segments which continue to contract and develop pressure, and by passive characteristics of affected segments of the myocardium which no longer shorten during systole. As maximum stretching occurs, the end-diastolic and end-systolic segmental lengths become almost fixed. Thus, a slope evolves based on an increase in pressure generated by the normal myocardium, and the length changes of a segment already nearly maximally stretched. This is the basis for the paradoxical increase in the ESPLR slope. This study shows that in the presence of ischaemia, the end-systolic pressure-length relationship is no longer a valid index of contractility.

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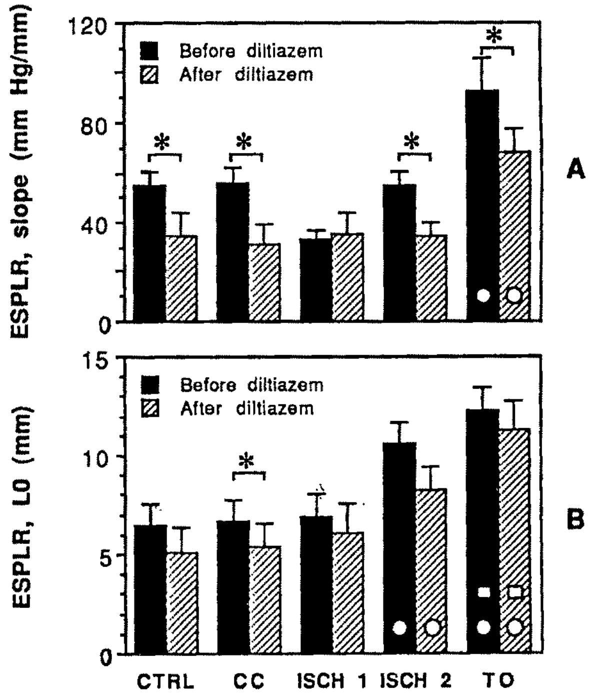

Fig. 1: ESPLR slopes (A) and ESPLR L0's (B) before and after D. Values are means, bar 1 SEM. * =P<0.05, comparing corresponding values before and after D; ○=P<0.05 compared to CTRL; □=P<0.05 compared to ISCH2.

Title:
ELECTROMYOGRAPHIC RESIDUAL EFFECTS AFTER MECHANICAL RECOVERY FROM NEUROMUSCULAR BLOCKADE

Authors: Goldman E. M.D., Malone M, B.S., Gupta B, M.D.
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Introduction Relative depression of simultaneous electromyographic (EMG) and mechanomyographic (MMG) responses during neuromuscular blockade (NMB) is still controversial and probably drug-specific[1]. In fact, EMG appears to be depressed more than MMG both under inhalation anesthetics[2] and during recovery from alcuronium NMB without halogenated agents[1]. Data on recovery from single bolus, vecuronium-induced NMB measured by EMG and MMG during isoflurane anesthesia is lacking. Therefore, we compared the EMG and MMG changes during isoflurane anesthesia with and without vecuronium to study whether the EMG lags behind the MMG after extubation.

Methods Nineteen patients were studied during their elective surgery after obtaining institutional approval and informed consent. Twitch tension of the adductor pollicis muscle to ulnar nerve stimulation was measured with a Grass FT-10 linear force transducer attached to a splint which kept the patient's arm immobilized. Preload tension of the transducer coupled to the thumb was 200-300g and remained constant. The EMG of the hypothenar eminence of the same hand was simultaneously recorded using a Datex NMT-221 neuromuscular transmission monitor. Supramaximal nerve stimulation (pulse width 110 Hz, constant current 0-70 mA range) and train-of -four (0.1 ms square-wave impulse at 0.5 Hz and repeated every 20 seconds for the duration of the study) were delivered over the ulnar nerve via surface electrodes.

Anesthesia was induced with thiopental 3 - 5 mg/kg and midazolam 1 - 3 mg i.v. Baseline values for EMG and MMG were obtained after loss of consciousness. An intubating dose of succynilcholine (1 mg/kg, Group 1, n=6) or vecuronium (0.1 mg/kg, Group 2, n=13) was then given followed in both groups by isoflurane in N_2O-O_2 for maintenance. Spontaneous recovery of first twitch over control (T1/T0) and train of four fade (T4/T1) were recorded every 20 seconds until the patient was awake and extubated, after reversal of vecuronium-NMB (peak recovery).

Results Peak recovery levels for EMG and MMG are shown in the table below along with the p value for testing mean difference between groups. The groups' MAC-hours of isoflurane were similar (group 1, 0.894 ± 1.17 and group 2, 0.895 ± 0.60).

PEAK RECOVERY VALUES FOR EMG AND MMG

	Group 1	Group 2	p
EMG T1/T0	83±3	65±4	0.01
EMG T4/T1	97±3	87±8	ns
MMG T1/T0	112±11	123±9	ns
MMG T4/T1	91±4	84±5	ns

mean ± SEM

Discussion Mechanical responses (T1/T0 and fade) and electrical fade fully recovered in both groups. EMG T1/T0 showed only partial recovery in group 1, which might be related to a prejunctional blocking action by isoflurane[3]. Even further depression of EMG T1/T0 in group 2 suggests that this prejunctional effect of isoflurane was increased by vecuronium. This electrical response coincided with full clinical and mechanical recovery (muscle strength and complete absence of fade) and indicates that the electromyogram may overestimate the degree of neuromuscular blockade.

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Title: COMPARISON OF ORAL TRANSMUCOSAL FENTANYL CITRATE (OTFC) WITH ORAL MEPERIDINE, DIAZEPAM, AND ATROPINE AS A PREMEDICANT IN CHILDREN WITH CONGENITAL HEART DISEASE*

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Introduction: An ideal agent for premedication has yet to be developed. Effective premedication can facilitate a safe and smooth anesthetic induction. Intramuscular injections (IM), though more predictable than oral premedications, create fear and anxiety in children (1). Fentanyl lollipops (OTFC) with transmucosal oral absorption is a non-threatening, alternative method of premedicating children. To date, all OTFC studies have involved healthy ASA I and II pediatric patients (2). The purpose of this comparative study was to evaluate the effectiveness of OTFC and oral meperidine, diazepam, and atropine premedication in children about to undergo surgical repair of congenital heart defects.

Methods: After approval from the Human Rights Committee, the FDA, and written informed consent from the patient's parents were obtained, 40 children between the ages of 2 and 12 years, ASA II and III with congenital heart disease, who were to have elective cardiovascular procedures were randomly divided into two equal groups. Group 1 received 0.4 ml/kg oral solution of meperidine (1.5 mg/kg), diazepam (0.2 mg/kg), and atropine (0.02 mg/kg) and a placebo lollipop while patients in group 2 received a 0.4 mg/kg placebo oral solution and a fentanyl lollipop (20-25 µg/kg fentanyl citrate). Thus all patients received some form of premedication. With the patient's parents in attendance, the premedication was administered in a double-blinded manner at least 30 minutes prior to the induction of anesthesia. Vital signs including systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), and respiratory rate (RR) were recorded at baseline (prior to premedication administration) and at ten minute intervals. Oxygen saturation (SpO_2) was monitored continuously. Every 10 minutes, the child's level of activity, apprehension, and cooperation was evaluated. Ease of separation from parents and of anesthetic induction were recorded; the scale used was 1: patient unafraid, cooperative or asleep, 2: slight fear and/or crying, quiet with reassurance, 3: moderate fear and crying, not quiet with reassurance, 4: crying, need for restraint. At the conclusion of the premedication period, the attending anesthesiologist assigned to the case gave additional premedication if deemed necessary. Side effects and duration were noted. Chi-square test, t-test, Barlett's test, Mann-Whitney statistics, and repeated measures analysis of variance were utilized. Significance was assumed at $p < 0.05$.

Results: Patients in the two groups were similar regarding weight, age, sex distribution, and baseline hemodynamics. One child (2.5 years old) refused both the lollipop and the oral solution and was removed from the study. Eight children (20%) chewed a portion of the lollipop. Otherwise, all children accepted the lollipop 11 (27.5%) required encouragement; 15 (37.5%) required coaxing to take the oral solution. Time between premedication and separation from parents varied from 30 to 100 minutes. HR showed no significant trends over time while SBP, DBP, and RR showed decreases, though not clinically significant, in both groups. SBP and DBP for all patients and SpO_2 and RR of acyanotic patients were statistically lower in group 2. Concerning children with cyanotic heart disease and SpO_2, group 1 (5 patients), 80% increased and 20% decreased SpO_2, whereas group 2 (2 patients), 100% increased SpO_2. Group 2 had significantly more patients drowsy between 30 and 60 minutes and had greater decreases in activity and apprehension scores from baseline. Emotional status at separation from parents and during induction were not significantly different between the groups. At separation from parents, 85% of group 2 and 80% of group 1 had scores of 1 or 2. At induction, 70% of group 2 and 80% of group 1 had scores of 1 or 2 (see graphs 1 and 2). The incidence of side effects in group 2 was 65% (13) nose itching, 10% (2) body itching, 25% (5) nausea, and 30% (6) vomiting. In group 1, 10% (2) had nose itching and 5% (1) complained about a dry mouth. Two children (10%) in group 2 experienced $SpO_2 < 90\%$ and required supplemental oxygen. No child in group 1 required oxygen treatment. One child in each group was deemed to be insufficiently sedated by the attending anesthesiologist and required supplemental premedication.

Discussion: OTFC (20-25 µg/kg) is effective at reducing preoperative anxiety and apprehension in children. Hemodynamics in children with congenital heart disease remained stable, however two children receiving OTFC required oxygen to treat a low SpO_2. Emotional scores at separation from parents and during induction were similar to those with oral meperidine, diazepam, and atropine. With high dose OTFC, side effects of nausea, vomiting, and pruritis were more pronounced. Other studies, involving healthy ASA I and II patients in which various doses of OTFC (5-25 µg/kg) (3) were used, it appears that higher dose OTFC results in considerably more side effects than lower dose OTFC. At present, we cannot recommend the high dose (20-25 µg/kg) OTFC as a premedication for children with congenital heart disease.

In patients with congenital heart disease studies evaluating the efficacy of lower doses are needed. If higher doses of OTFC should be needed, then a concomitant antiemetic should be considered.

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*Supported by Anesta Corporation.
**Department of Anesthesia, Washington University, St. Louis.

CHART 1 - INDUCTION

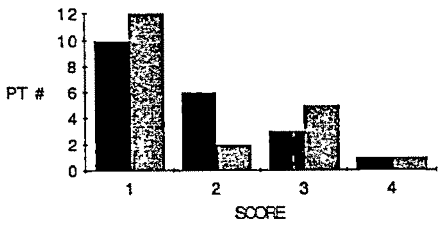
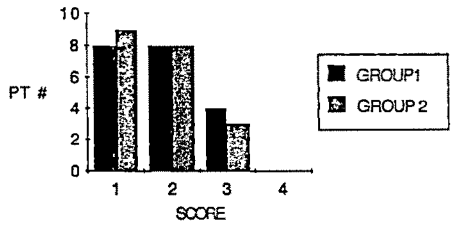


CHART 2 - SEPARATION



Title: ORG9426 POTENTIATES NEUROMUSCULAR BLOCKING EFFECTS OF OTHER NONDEPOLARIZING MUSCLE RELAXANTS IN RATS

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Introduction. It has been reported that in *in vitro* experiments (1) and in clinical studies (2,3) d-tubocurarine (d-Tc) or metocurine potentiated the neuromuscular (NM) blocking effects of pancuronium (PANC), vecuronium (VEC) and atracurium. In this study the *in vitro* NM effects of all possible combinations of ORG9426, pipecuronium (PIPEC), PANC and VEC were investigated. ORG9426 and PIPEC are undergoing clinical investigation at this time. For sake of comparison the interaction of these 4 steroid type muscle relaxants (MR) with d-Tc were also investigated.

Methods. This investigation was approved by our Institutional Animal Investigation Committee. The phrenic nerve-hemidiaphragm preparations of male Sprague-Dawley rats were suspended in organ baths filled with modified Krebs' solution (4) of 37°C, bubbled with 95% O_2 - 5% CO_2. The hemidiaphragms were stimulated indirectly with supramaximal square wave impulses of 0.2 ms duration at 0.1 Hz. The force of contraction of the muscle (P) was quantitated by transducers and continuously recorded. After P became stable, in some experiments, the cumulative dose-response of the five muscle relaxants (MR) was determined and from the best fit log dose-response regression line the IC50 values were calculated. In other experiments a half of the IC50 concentration of one of the five MR was added to the bath and after the development of its maximal NM effect, the dose-response of one of the other MR was determined. This was done with all possible combinations of the 5 MR.

Results. The addition of the IC50/2 concentration of any of the five MR produced 5 to 10% NM block. The IC50 of each of the MR was significantly decreased by the addition of the IC50/2 of any of the other four MR (see table; $p < 0.01$ as determined by ANOVA followed by Dunnett's test). Isobolograms constructed from the IC50 values (some examples shown in figure) indicated that ORG9426 and d-Tc potentiated the NM effect of each other and that of the three other MR. The greatest potentiation was with ORG9426 - d-Tc combination. VEC and PIPEC potentiated the NM effect of each other, but there was no potentiation in the NM effect of PANC-VEC, PANC-PIPEC combinations.

Discussion. It appears that the preliminary addition of d-Tc or ORG9426 causes greater potentiation than "priming" with any of the three other MR. The greatest potentiation was observed between ORG9426 and d-Tc. Similar observations were reported earlier with regard to d-Tc (5). It is conceivable that the greater potentiation by ORG9426 or d-Tc is caused by the greater inhibition of the positive nicotinic feedback mechanism of the evoked release of acetylcholine. The mutual potentiation between d-Tc and ORG9426, if confirmed in man, may have clinical significance.

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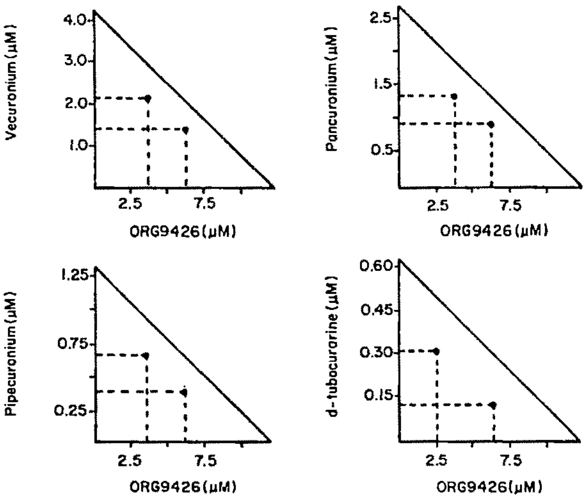
IC50 values of 5 muscle relaxants (MR) alone and preceded by 0.5 x IC50 of other MR.

		IC50 (μM)				
	Alone	preceded by 0.5 x IC50 of				
		ORG9426	VEC	PANC	PIPEC	d-Tc
ORG9426	12.43*	-	3.68	3.77	3.44	2.43
VEC	4.40	1.49	-	2.55	1.72	1.59
PANC	2.68	0.92	1.24	-	1.21	0.60
PIPEC	1.35	0.42	0.37	0.55	-	0.55
d-Tc	0.62	0.12	0.27	0.19	0.25	-

*Mean of 4 experiments, SEM not shown for lack of space.

ORG9426 and d-Tc potentiated the NM effect of each other and that of the 3 other MR. Potentiation was greatest with ORG9426 - d-Tc combination.

ISOBOLOGRAMS OF THE INTERACTIONS OF ORG9426 WITH OTHER NONDEPOLARIZING MUSCLE RELAXANTS



TITLE: THE VALIDITY OF A COMPUTED ESTIMATE OF HEMATOCRIT AND BLOOD VOLUME DURING MAJOR BLOOD LOSS.

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INTRODUCTION

I devised a BASIC program to estimate blood volume and composition during surgery which involves major blood loss. The program calculates an estimate of original blood volume, plasma volume and red cell volume from the patient's weight and original hematocrit using simple equations:

$$V_{blood} = Wt*F,$$
$$V_{blood} = V_{rbc} + V_{plasma},$$
$$Hct = 100*(V_{rbc}/V_{blood}),$$

where the Vs are volumes of blood, red cells, and plasma, Hct is hematocrit, and F is an operator selected factor.

During the course of surgery the operator enters blood lost and fluids replaced as these occur. The program assumes that each loss occurs at the then current hematocrit and apportions the loss between the plasma volume and the red cell volume. New volumes are displayed as they are computed. When fluids are administered these volumes are entered by the operator, and the program apportions these between plasma and red cell volumes. Whole blood is assumed to have an hematocrit of 30% and a volume of 480 cc, while packed cells are given an hematocrit of 50% and a volume of 250cc. Washed red cells scavenged and returned to the patient from Cell Saver are assumed to have an hematocrit of 60% and a volume of 125 cc. One third of the volume of administered saline and the entire volume of administered hydroxyethylstarch are assigned to plasma volume. Based on these assumptions the program calculates new blood, plasma, and red cell volumes and a new estimated hematocrit. An "undo" feature permits the operator to see the result of a putative fluid administration and then erase the act.

This study was carried out to assess the accuracy of these computations. Since no simple method exists for quantifying blood volume, only computed hematocrit was compared with measured hematocrit.

METHOD

After approval for chart review was obtained from our institutional committee, charts were selected from cases done in the past year. Twenty three charts were found where the blood loss was greater than 10% of estimated blood volume, and both a computer estimate of hematocrit and an immediate post-operative laboratory determination of hematocrit were available.

RESULTS

Blood loss ranged from 10 to 51% of estimated blood volume. The hematocrit estimated at the end of surgery was compared with that obtained by the clinical laboratory immediately following the procedure. The figure shows the plotted data (there are 21 data points since two pairs of values were duplicates). The data have less scatter at lower values of hematocrit than at higher values. On sixteen occasions the values were within 2 hematocrit points of each other. A linear regression analysis of these pairs of data yielded the following equation:

$$Hct_{lab} = 3.2 + 0.89*Hct_{est},$$

where the Hct values are those determined by the clinical laboratory and by the computer program.

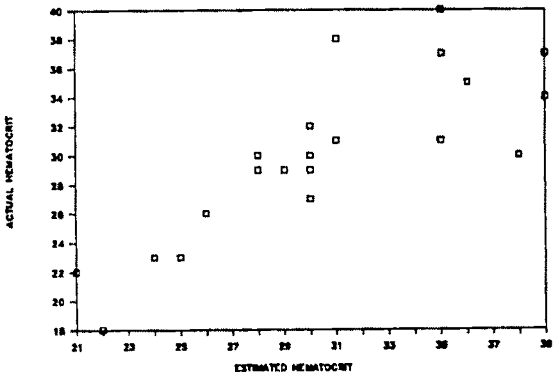
Pearson's Correlation coefficient was 0.82 for the paired values indicating a probability of less than 0.0000017 that the values are unrelated.

DISCUSSION

These data revealed a high degree of correlation between estimated and determined hematocrit in spite of the simplicity of the computations and assumptions and the known inaccuracies of clinical determinations of blood loss (measuring aspirated blood and weighing surgical sponges).

Having estimates of blood volume and hematocrit simplifies selection of appropriate fluids for replacement during the course of surgery, and reduces the need for invasive estimates of volume. Of course any single parameter, whether measured or computed must be evaluated in the light of other relevant information.

COMPUTED VS ACTUAL HEMATOCRIT



Title: HISTAMINE RELEASE FROM SHORT AND INTERMEDIATE ACTING MUSCLE RELAXANTS IN ADOLESCENTS

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Introduction

It has been our clinical impression that transient cutaneous reactions occur more frequently in adolescents than in children after the administration of muscle relaxants. Also, we have observed transient maculopapular rashes following succinylcholine. To evaluate the importance of histamine in these cutaneous reactions, we measured plasma histamine levels after the administration of succinylcholine, atracurium or vecuronium in adolescents.

Methods

The study was approved by the human studies committee of our institution and a written consent was obtained from the parents and the patients. Twenty-seven ASA 1 adolescents 12-19 y were evaluated. Preoperative sedation was midazolam 1-2 mg. Anesthesia was induced by iv thiopental 5-10 mg/kg. For sampling purposes, another iv cannula was inserted in the antecubital vein of the opposite arm of the iv, and a control blood sample was obtained from the cannula after the administration of thiopental. At random, one of the following muscle relaxants was administered in the first iv in less than 5 sec, atracurium 0.6 mg/kg, succinylcholine 1.5 mg/kg or vecuronium 0.12 mg/kg. Two min after the relaxant, a second blood sample was obtained from the opposite side and the endotracheal tube was inserted. Five min following the relaxant, a third blood sample was obtained. All patients were observed carefully for the occurrence of skin reactions.

The blood samples were kept on ice in dry heparinized tubes, cold centrifuged in less than one hour and frozen. A radioenzymatic assay using highly purified histamine n-methyl transferase was used to determine the plasma histamine levels (1). Each sample was assayed in duplicate with its own internal standard. Data were analyzed by student t test and was considered significant when $p<0.05$.

Results

Twenty-seven adolescents in 3 equal groups were evaluated. The mean age was 15.6±0.4 y (mean ± SE) and the mean weight was 55.8±3.4 kg. The incidence and the severity of cutaneous reactions was more frequent following atracurium or succinylcholine than vecuronium (Table 1).

Table 1

Incidence of Cutaneous Reactions Following the Administration of Muscle Relaxants in Adolescents

	Mild flush	Marked flush	Maculopapular Reaction
Atracurium (n=9)	3	2	1
Succinylcholine (n=9)	5	1	1
Vecuronium (n=9)	3	-	-

There was no significant change in the the mean pulse rates and blood pressures in the three groups of patients studied. Nor was there a clinically significant (>15%) change in the cardiovascular parameter in any one of the patients.

The determination of plasma histamine levels in patients receiving vecuronium was unreliable, possibly due to interference of vecuronium with the enzyme histamine n-methyl transferase. Consequently, the histamine data on vecuronium receiving patients were discarded. The data on succinylcholine and atracurium correlated with the internal standards and are reported in Table 2.

Table 2

Mean Plasma Histamine Levels (pg/ml) in Adolescents Receiving Atracurium and Succinylcholine

	Control	2 min after	5 min after
Atracurium	329.1±137.2	578.1±215	789.3±481.5
(Range)	(80-1409)	(159-1840)	(133-4669)
Succinylcholine	238.5±42.8	221.1±46.8	199.4±29.2
(Range)	(54-305)	(77-275)	(93-246)

There was a tendency to note a rise in plasma histamine levels in patients receiving atracurium but the difference was not statistically significant because the rise was only in a few patients. In the succinylcholine patients no such tendency was noted. Two patients receiving atracurium showed more than a 10 fold rise in plasma histamine levels; these patients had marked skin reactions. However, not all patients that had skin reactions had a rise in plasma histamine levels. In succinylcholine patients, none of the patients with skin reactions had a rise in plasma histamine levels.

Discussion

The data indicate that histamine release from atracurium is rather similar in adolescents and children (2). Its occurrence is due to incidental phenomenon occurring in few of them, whereas in adults it occurs in a predictable pattern (3). In contrast to atracurium, succinylcholine skin reactions in adolescents do not relate to plasma histamine release; their exact cause requires further investigation.

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3. Scott RPF, Savarese JJ, Basta SJ et al. Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response. Br J Anaesth 57:550-553, 1985.

TITLE: **LUMBAR VERSUS THORACIC ADMINISTRATION OF EPIDURAL MORPHINE FOR POST-THORACOTOMY ANALGESIA**

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Introduction: It is believed that lumbar administration of epidural morphine (EM) produces effective analgesia for thoracic surgical procedures. A retrospective study found no difference in dosage, duration or quality of analgesia provided by EM regardless of the route of administration, lumbar or thoracic (1). We are unaware of any prospective study in post-thoracotomy patients that evaluated the effect of epidural catheter site on EM analgesia and pulmonary function following thoracotomy. We therefore compared the effects of thoracic and lumbar routes of EM administration.

Methods: Following institutional review board approval and informed consent, 20 patients undergoing thoracotomy for pulmonary resection were studied. All patients were premedicated with midazolam 2-5 mg i.m. Immediately prior to surgery, epidural catheters were placed via a midline approach via L2-L3 or L3-L4 interspaces (n=10) or T6-T7 or T7-T8 interspaces (n = 10). Only a test dose of local anesthetic was given after catheter insertion. Anesthesia was induced with pentothal and maintained with isoflurane in oxygen. EM 5 mg (0.5 mg/ml) was administered prior to surgical closure of the chest. All patients were extubated within 30 min of skin closure. In the recovery room, patients were given a single dose of epidural fentanyl (100-250μg), and EM in 3 mg increments as needed to render them comfortable. Patients were followed for 24 hours and additional 3 mg doses of EM were given as needed to achieve analgesia. Pulmonary function tests (PFTs) were done pre-operatively using a portable electronic pneumotachometer and tests were repeated 24 hours post-operatively. Vital capacity (VC), forced vital capacity (FVC), forced expired volume in one second (FEV$_1$), and peak expiratory flow rate (PEFR) were measured. The best of three efforts was used for each test, and the ratio of post-operative/pre-operative values was calculated. At 24 hours patients were asked to grade their pain on a visual analogue scale, and somnolence was assessed with a 0 - 4 scale (0-awake; 1-occasionally drowsy; 2-frequently drowsy; and 4-unresponsive). Both total EM amount and the number of injections required in 24 hours were noted. Results were expressed as mean ± 1SE and analyzed using t-test and X^2 analysis at $p < 0.05$.

Results: There were no differences in the two groups with regard to age, weight, height, or types of procedure. VC, FVC, FEV$_1$, and PEFR decreased significantly in both groups approximately 50%. However, the percent decrease did not differ significantly between the groups (Fig 1). Somnolence scores were not significantly different between the groups but pain scores were lower in the thoracic group (Fig 2). The total number of doses as well as the 24 hr total EM requirement were significantly lower in the thoracic group (Fig 2). No patient required treatment for respiratory depression.

Discussion: It appears from our data that the thoracic route of EM administration produces more effective analgesia for post-thoracotomy patients than does the lumbar route. The reason for this may be related to the high concentration of EM reaching the opioid receptors in the thoracic spinal cord. The diminished dose requirement may help decrease the number of post-operative interventions. The severe deterioration of PFTs following thoracotomies has been observed by other authors. Our data shows this decrease in PFTs remains unaffected by the route of EM administration.

Reference: 1. Fromme GA, Steidl LJ, Danielson DR. Comparison of lumbar and thoracic epidural morphine for relief of postthoracotomy pain. Anesth Analg 1985;64:454-5.

Figure 1: Post-operative pulmonary function tests. No significant differences between groups.

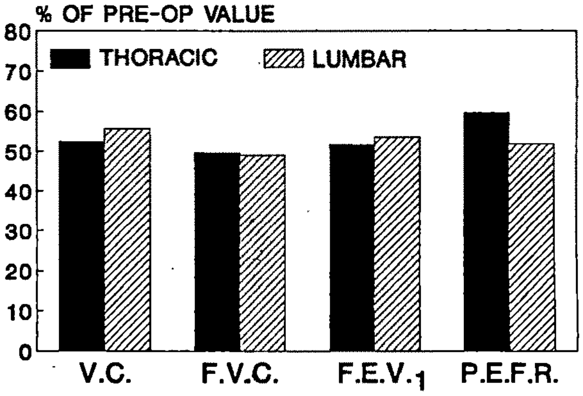
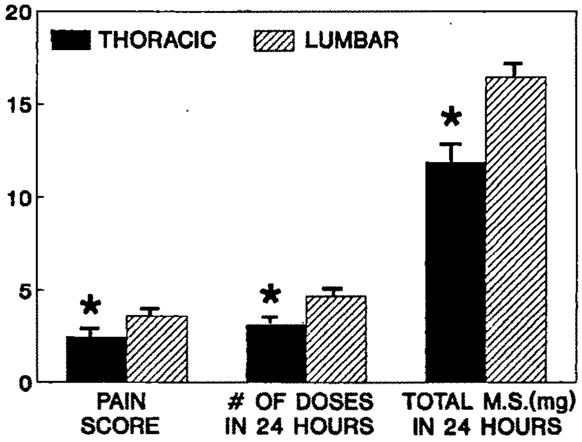


Figure 2: Pain scores and epidural morphine dose requirement. * = significantly different from lumbar group.



TITLE: PREDICTIVE VALUE OF COAGULATION TESTING AFTER CARDIOPULMONARY BYPASS

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INTRODUCTION: Many laboratory tests are used to diagnose coagulopathies after cardiopulmonary bypass (CPB) (1). The present study prospectively evaluated the values of several standard laboratory coagulation tests in predicting increased blood loss following CPB. In addition, an earlobe (Duke's) bleeding time (EBT) was used to detect decreased platelet function.

METHODS: After approval by the institutional review board and informed consent from each patient, 881 consecutive cardiac surgical patients (668 CABG, 187 valves, and 26 reoperative CABG or valve patients) were studied over approximately 18 months. Most were managed with bubble oxygenators, and heparin was administered to maintain activated coagulation time (ACT) > 400 seconds during CPB. The following laboratory tests were performed using standard techniques both preoperatively and after confirmation of complete post-CPB heparin neutralization (by automated protamine titration): ACT, activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (Fib), fibrin(ogen) degradation products (FDP), platelet count (Plt) and EBT. Spearman's rank correlation (r) and multiple stepwise regression techniques assessed correlations between laboratory tests and 16-hour mediastinal blood drainage (16 hr BL), considering $P<0.05$ significant. CABG, valve, and reoperation patients were analyzed as separate groups. Other variables such as age, sex, and CPB duration were included in the multivariate analysis. Patients requiring postoperative re-exploration for bleeding were excluded only if a surgical bleeding site was found.

RESULTS: Table 1 shows 16 hr BL and laboratory correlations with 16 hr BL by group. Stepwise regression in the CABG group accepted sex, APTT, Fib, and age as 16 hr BL predictors, yielding a cumulative coefficient of determination (R^2) of 0.10. In the valve group, stepwise regression accepted sex, CPB duration, Plt, and FDP for a cumulative R^2 of 0.22. Separately analyzing the 10% of CABG and valve patients having the highest 16 hr BL did not importantly alter the findings, nor did separately analyzing the change in coagulation tests from the preoperative to post-CPB values. Males experienced greater ($P < 0.05$) 16 hr BL even after correcting for body weight and body surface area. The reoperation group was judged too small for stepwise regression.

DISCUSSION: Large numbers of patients permit weak associations to reach statistical significance, as shown in Table 1. The findings suggest that APTT and Fib best predict increased blood loss in CABG patients, while Plt and FDP serve best in valve replacement patients. EBT and TT have no predictive value. Stepwise regression methods reached statistical significance, but cumulatively explained only 10 and 22% of 16 hr BL in CABG and valve groups, respectively. In conclusion, extensive coagulation tests (including an earlobe bleeding time) poorly predict postoperative bleeding when analyzed individually or collectively. Aside from documenting heparin neutralization, routine use of coagulation tests post-CPB appears unjustified.

REFERENCE:

1. Bick RL, Sem Thromb Hemostas 1985; 11:249.

TABLE 1:
PREDICTORS OF 16 HR BLOOD LOSS AFTER CPB

CABG Group

16 hr BL 770 ± 429 ml

	r	P-value
APTT	0.22	.0001*
Fib	-0.14	.0003*
Plt	-0.08	.051
ACT	0.07	.053
PT	0.06	.12
EBT	0.04	.34
FDP	0.01	.73
TT	0.01	.88

Valve Group

16 hr BL 761 ± 504 ml

	r	P-value
Plt	-0.21	.006*
FDP	0.21	.006*
ACT	0.19	.013*
PT	0.15	.047*
APTT	0.12	.13
Fib	-0.09	.23
TT	0.08	.32
EBT	0.01	.95

Reoperation Group

16 hr BL 725 ± 474 ml

	r	P-value
ACT	0.47	.015*
EBT	-0.31	.15
Plt	-0.20	.32
APTT	0.16	.44
PT	0.13	.53
TT	-0.10	.64
Fib	-0.07	.75
FDP	0.04	.85

* statistically significant

TITLE: HEMODYNAMIC CHANGES DURING INDUCTION OF ANESTHESIA IN HEART TRANSPLANT RECIPIENTS

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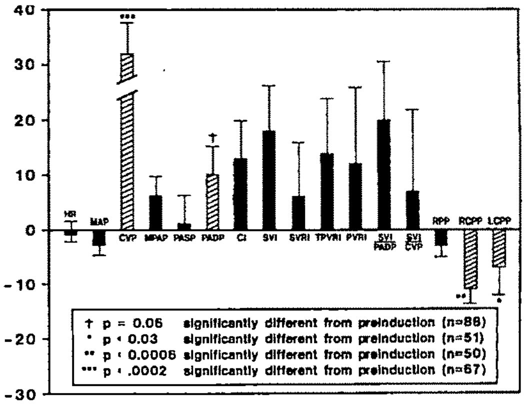
Introduction: This study is based on our clinical and hemodynamic heart transplant data base (1884-88). This report examines hemodynamic changes during induction of anesthesia (I).

Methods: 104 recipients (NYHA Class IV, male/female ratio 3, 46 ± 1 years, [mean ± SEM], 71 ± 2 kg, 1.82 ± .03 m^2 BSA, ischemic cardiomyopathy 44%, primary cardiomyopathy 51%, others 5%; EF 19 ± 1%, PVRI 346 ± 22 dynes cm^{-5} sec m^2) were premedicated [Lorazepam® (10-30 ng/kg) and Cyclosporine A (5 mg/kg)] and monitored (arterial line and pulmonary artery catheter). O_2 and other supportive therapy were maintained, adjusted or added before I. Awake intubations (n = 15) were carried out after anesthetizing the airway (lidocaine 4%) under sedation (fentanyl 1-2 mcg/kg). I agents (ketamine [1-3 mg/kg], etomidate [.1-.3 mg/kg], midazolam [.1-.3 mg/kg] fentanyl [10-20 mg/kg], sufentanil [1-2 mg/kg]) titrated to unconsciousness allowed a modified rapid sequence intubation with cricoid pressure (n = 89) after either pancuronium or vecuronium (.1 mg/kg). Recipients were ventilated (IPPV-PEEP = 5 cm H_2O, ET CO_2 , < 38 torr) and administered isoflurane (.15-.25% ET) in O_2, FiO_2 = 1.0. Hemodynamic profiles, pre- and post I, included: HR (bpm), SAP (mmHg), DAP (mmHg), MAP (mmHg), CVP (mmHg), PADP (mmHg) and/or PAWP (mmHg, only recipients with prothrombin time < 13.5 sec) CO_{TD}, blood gases, temp (°C) and hemoglobin (Hgb g%), Na+, K+, (mEq/l) and calculated CI l/min/m^2 BSA, SVI (ml/beat/m^2), TPVRI, PVRI, SVRI (dynes cm^{-5} sec m^2), indices of left (SVI/PADP ratio) and right (SVI/CVP ratio) ventricular performance, $\Delta\bar{G}$ PADP-PAWP, RPP and coronary perfusion pressures for the left (LCPP = DAP - PADP, mmHg) and right (RCPP = DAP - CVP, mmHg), coronary arteries. Unpaired two-tailed t, paired t, Wilcoxon-Signed-Rank and Chi-square (Yates) tests were used to determine signficance.

Results: Profiles before I were: HR 97 ± 2, MAP 86 ± 2, CVP 13 ± 1, MPAP 35 ± 1, PADP 26 ± 1, PAWP 28 ± 1, $\Delta\bar{G}$ PADP-PAWP 1 ± 1, CI 2.12 ± .07, SVI 23 ± 1, SVRI 2738 ± 152, TPVRI 1448 ± 57, PVRI 346 ± 22, SVI/PADP 1.01 ± .07, SVI/CVP 2.95 ± .38, RPP 11076 ± 288, RCPP 57 ± 2, LCPP 45 ± 2. At 37° C, post I gases were: pHa 7.46 ± .01, $PaCO_2$ 34 ± 1 mmHg, PaO_2 300 ± 15 mmHg, CO_3H^- 24 ± .4 mEq/l. Pre I Hgb, K^+ and Na^+ were 13 ± .2 gms%, 4 ± .1 mEq/l, 134 ± 1 mEq/l, respectively. Bar graph (Fig) depicts percent changes from pre I for all variables; only the rise in CVP (53 ± 17%), p < 0.001), and fall in RCPP (-11 ± 3, p < .006) and LCPP (-7 ± 5%, p < 0.03) were significant. During I, hemodynamic measurements indicated the need for inotropic or vasodilator support in 46 and 60 of 104 recipients, respectively. Whereas, recipients with a CI ≤ 2 before induction (Group I, n = 20, CI 1.6 ± .04) experienced a rise in CI: (47 ± 12%, p < .01) those with a CI > 2 (Group II, CI 2.6 ± .07, n = 26) experienced a fall (-13 ± 6%, p < .01), to similar post I CI values (GI 2.3 ± .18, GII 2.3 ± .14).

Discussion: Inotropic and particularly vasodilator support or both was needed before and during the induction of most heart recipients in whom a rise in cardiac filling and fall in coronary perfusion pressures were the only significant changes. With pharmacological support, guided by measuring CI, the outcome of induction, was the same among recipients with critically low (GI: CI ≤ 2) or decreased, but yet acceptable (GII: CI > 2), preinduction CI.



TITLE: THE ROLE OF LOCALIZED P31-MRS AND EEG FOR STUDIES OF HYPOXIA IN THE CAT BRAIN

AUTHORS: BL Grundy, MD, KN Scott, PhD, WE Ballinger, MD, WP Kuan, MS, AI Webb, PhD, AW Bauman, REegEpT, JM Beaty, BS

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INTRODUCTION: Hypoxia is a constant threat during anesthesia and may contribute to neurologic injury in anesthetized or critically ill patients. Although numerous studies of cerebral ischemic hypoxia have been reported, little has been done to investigate the cerebral effects of hypoxia without ischemia. We developed a model for studies of hypoxia in cats, using EEG and localized P-31 MRS. We correlated the EEG and MRS changes with duration of hypoxia, clinical neurologic outcome, and histopathology.

METHODS: With approval of our institutional animal investigation committee, seven cats, previously implanted under anesthesia with a chronic arterial catheter with a subcutaneous port, were studied. The animals were anesthetized with isoflurane, intubated, and ventilated. Ag/AgCl cup electrodes were attached with collodion. After instrumentation, vecuronium was given for chemical restraint and the isoflurane was withdrawn. After 1 hour, hypoxia was induced. Both EEG and MRS were recorded before and during hypoxia and during and after resuscitation with 100% O_2. MR was obtained with a SIS, Inc. model VIS spectrometer. A half-saddle coil double-tuned to H-1 and P-31 was used. H_o homogeneity was adjusted by shimming on the H-1 signal. Localization by the ISIS technique gave a localized volume of 6.5 cc, or larger, which was always totally within the brain. Spectral acquisition time was 14 min. The peak areas were determined by planimetry and the pH from the chemical shift of Pi from PCr.

From our previous studies with 9 cats, we had concluded that if systemic effects of hypoxia are allowed to progress to the point of cardiovascular collapse, the cat may not survive. It seems likely that acute severe hypoxia produces death by cardiovascular, rather than neurologic mechanisms. However, by providing a constant infusion of bicarbonate to prevent systemic acidosis and a brief period of elevated O_2 to rescue the heart from the systemic effects of hypoxia, neurologic abnormalities and histopathological changes in the brain can be produced by 8% inspired O_2, yet death is avoided. During ventilation with 8% oxygen, four cats were given 100% O_2 for 15 seconds when arterial blood pressure fell to 60 mmHg. Because of considerable variability in the number of O_2 rescues required and the duration of hypoxia tolerated by the cats, we gave 3 cats 10% O_2 for 1 minute at intervals of 10, 15, or 20 minutes.

RESULTS: Hypoxia produced increases in Pi and decreases in PCr, pHi, PCr/Pi, and progressive slowing of EEG. Neurological deficits were seen after hypoxia, which partially resolved over the next week. One week after hypoxia, the EEG and MRS were recorded and the animal sacrificed. Periventricular white matter injury was detected with light microscopy, while both cortical and subcortical gray matter were spared.

The results in the first 4 cats are summarized in Table 1. Total pathology reflects semiquanitative ranking of the pathology, with zero being normal. The EEG score, (0=normal), is a semiquantitative integrated score derived from visual analysis and 6 standard EEG pattern descriptors (2). A Spearman rank correlation coefficient analysis for PCr/Pi and pH during hypoxia showed perfect rank order with duration of hypoxia. EEG scores showed perfect rank order with pathologic scores. PCr/Pi returned to near control values 1 hour post-hypoxia, but was greatly reduced 7 days post-hypoxia.

Table 1

			PCr/Pi@					
Cat	Min.	Hypo			Post-Hypox.		Hypo	Total
No.	8%O_2	EEG	Cont	Hypo	1 Hr	7 Day	pH&	Path.
11	101	6.11	3.67	1.84	3.64	1.81	6.40	18
10	70	5.41	2.74	1.91	2.56	2.10	6.65	11
14	124	5.01	3.57	1.30	3.27	2.75	6.24	7
13	60	1.41	3.41	2.90	3.89	2.04	7.07	0

@ Range ±0.3; & Range ±0.04

The changes observed in the last 3 cats are different from those in the first 4. However, 1 minute of 10% O_2 every 15 minutes allowed us to keep the cat hypoxic for 3 hours and produced an EEG score 4.51 and total pathology score of 15. This appears to be our most favorable model.

DISCUSSION: We conclude that reproducible neurological abnormalities and histopathological changes in the brain can be produced in cats with hypoxia in the absence of ischemia. Both EEG and P-31 MRS reflect hypoxic changes. Our model will need further refinement and validation. However, there are no comparable models of hypoxic injury without ischemia. Cerebral white matter edema is seen in high altitude sickness (1), and white matter injury with sparing of the gray has been described in critically ill patients. With the advent of CT and MRI, it has become apparent that deep white matter lesions are common in demented patients(2,3). Hypoxia during and after anesthesia might contribute to dementia in elderly patients. Because our model is non-invasive and does not require anesthetic agents during hypoxia, it is uniquely suited for exploration of the effects of various anesthetics and resuscitation techniques on the hypoxic brain.

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TITLE: DROPERIDOL DECREASES VOMITING AFTER TONSILLECTOMY AND ADENOIDECTOMY IN CHILDREN

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Introduction: Droperidol has been used effectively to decrease the incidence of vomiting following strabismus surgery. A recent survey identified children undergoing tonsillectomy and ademoidectomy as having 60% incidence of vomiting in the first 6 hours following surgery (1). Reducing the incidence of vomiting is of greater importance in this population of patients because of the close relationship of the operative site to the major airways. With the approval of the hospital human investigation committee we undertook a randomized double blind study to evaluate the potential utility of droperidol to decrease this incidence of post operative vomiting in this group of patients.

Methods: After obtaining parental consent 79 ASA PS, I and II patients aged 1.5 to 18 years were randomized to receive either droperidol 50 µg/kg i.v. or saline immediately following the induction of anesthesia. All patients received an oral premedication containing meperidine-atropine-diazepam. The anesthetic technique was limited to inhalation induction using halothane and nitrous oxide in oxygen, muscle relaxation with vecuromium and intravenous morphine 0.1 mg/kg. The times from the completion of surgery to extubation and until arrival in the PACU, and the duration of PACU stay were recorded. All episodes of vomiting were noted from the time of arrival in the recovery room until discharge from the hospital the following day. Differences between groups were tested using Chi square analysis for nominal data, and Student's t-test for interval data. A $p < 0.05$ was considered significant.

Results: There was no difference in the basic demographics of the two groups (Table 1). Few patients in either group vomited in the recovery room, but vomiting frequently occurred after arrival to the inpatient ward (Table 2). Only16 of 35 (46%) patients who received droperidol vomited compared to 31 of 44 (71%) control patients ($p < 0.04$). Not only did fewer patients in the droperidol group vomit, but those who vomited did so fewer times 1.9 ± 1.2 vs. 4.6 ± 3.8 ($p < 0.01$). (Figure).

Discussion: Droperidol was effective in reducing both the incidence of vomiting following tonsillectomy and ademoidectomy as well as in reducing the severity of vomiting as well. Despite the fact that the average time to first emesis was approximately 6.5 hours in the droperidol group multiple episodes of emesis were still more frequent among the control patients indicating that the anti-emetic effects of droperidol were prolonged in their action in this group of patients. There were no apparent side effects from using droperidol, and both groups had similar extubation and discharge times. It is possible that repeating the dose of droperidol might further decrease the incidence of vomiting.

TABLE 1. DEMOGRAPHIC DATA (mean ± S.D.)

Group	Control	Droperidol
N	44	35
Age (years)	6.1 ± 3.3	6.6 ± 4.1
Weight (kgs)	23.9 ± 13.1	29.3 ± 19.5
Sex M/F	25/19	18/17
Procedure		
Adenoidectomy	3	1
Tonsillectomy	3	1
Tonsill./Aden.	38	33
Time (minutes) from end of surgery to:		
Extubation	6.2 ± 4.3	6.9 ± 5.4
Arrival PACU	10.4 ± 5	11.7 ± 5.3
PACU stay (min)	99.6 ±18	97.4 ± 13

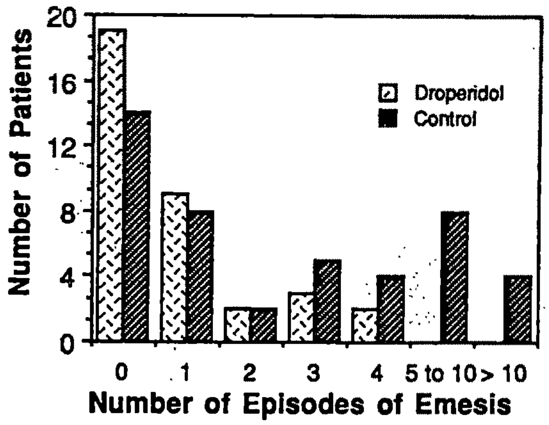
No significant statistical difference between the groups.

TABLE 2. POSTOPERATIVE EMESIS

	Control	Droperidol	P
Incidence of Vomiting (%)			
PAR	14	6	0.43
Floor	68	46	0.07
PAR + Floor	71	46	0.04*
Time to first emesis (min)	296 ± 192	388 ± 152	0.12
Episodes emesis in vomiters	4.6 ± 3.8	1.9 ± 1.2	0.01*

* Significant P Value

FIGURE



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Title: HEPATIC, MESENTERIC, AND SYSTEMIC CIRCULATORY CHANGES ACCOMPANYING HUMAN ORTHOTOPIC HEPATIC TRANSPLANTATION

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Introduction: Patients presenting for orthotopic liver transplantation [OLT] typically demonstrate a hyperdynamic circulatory state that includes an elevated cardiac output and decreased systemic vascular resistance resulting from peripheral A - V shunts. Varying degrees of portal hypertension are also present. As the diseased liver is replaced with a denervated graft having relatively normal vasculature, dramatic changes could be expected to occur in the enterohepatic circulation that may be reflected in systemic hemodynamics. The purpose of this study is to quantitate the steady state enterohepatic circulatory changes related to implantation of the graft, and to determine their influence upon systemic hemodynamics.

Methods: A retrospective study of 101 consecutive OLT's, 50 grafts preserved with Eurocollins solution [EC] and 51 preserved with University of Wisconsin solution [UW], was performed to elucidate the steady state enterohepatic and systemic circulatory changes that accompany hepatic transplantation. Portal and hepatic vein pressures [PVP,HVP] in the native and graft livers were measured by direct puncture using a 27 gauge needle connected to the CVP transducer. Hepatic artery and portal vein flows [HAF,PVF] were measured by electromagnetic flowmetry. Routine hemodynamic measurements (arterial, pulmonary artery and central venous pressures [HAP, PAP, CVP]; cardiac output[CO]; temperature) were acquired at the time of flow and pressure measurements. Measurements were obtained from the native liver approximately 30 minutes prior to removal, and from the graft liver at least 1 hour following complete revascularization (hepatic artery and portal vein). Flows were normalized to 100 grams of wet liver weight [HAFG,PVFG]. Hepatic artery and portal vein resistances were calculated and also normalized to wet liver weight [HARG,PVRG]. Systemic vascular resistance [SVR] was determined along with mesenteric, portal and hepatic artery perfusion pressures [MPP,PPP,HAPP]. Statistical significance was computed using ANOVA and paired Student's t test.

Results: The Table illustrates relevant enterohepatic and systemic hemodynamic parameters in the native and graft environment. The pressure drop across the portal vasculature [PPP] decreases in response to lower PVR of the graft resulting in a decreased portal vein pressure. The decreased PVP causes an increased MPP which in turn increases portal flow [PVF], venous return, and therefore cardiac output. The normalized hepatic artery flow decreases slightly from the elevated HARG in reflex response to increased PVF. There were no statistically significant differences in these data related to the preservation (EC vs UW) solution.

Discussion: Changes in the enterohepatic circulation, predominantly a lowered portal vein resistance, result in portal vein decompression with increased portal vein flow, and hence increased cardiac output in a patient with an existing hyperdynamic circulatory system. The magnitude of the PVF increase is related to the degree of portal hypertension. The obvious advantages of significantly decreased PVP to reduce or eliminate variceal bleeding and decrease venous collateral shunt flow outweigh the cost of a further increase in cardiac output. There have been no clinical difficulties associated with the management of a further increase in cardiac output following hepatic transplantation.

Table

	Pre-OLT	Post-OLT	signif.
MAP (mmHg)	73 ± 10	75 ± 10	NS
CO (L-min^{-1})	8.9 ± 3.5	10.4 ± 3.8	$p<.009$
SVR (dyne-s-cm^{-5})	663 ± 298	573 ± 254	$p<.0345$
PVP (mmHg)	25.1 ± 5.5	18.4 ± 3.6	$p<.0001$
HAF (ml-min^{-1})	488 ± 373	538 ± 269	NS
PVF (ml-min^{-1})	1184 ± 777	2288 ± 1162	$p<.0001$
HAFG (ml-min^{-1}-100gm^{-1})	31.9 ± 26.0	31.4 ± 17.5	NS
PVFG (ml-min^{-1}-100gm^{-1})	83.3 ± 64.6	136.6 ± 80.2	$p<.0001$
HARG (dyne-s-cm^{-5}-100gm^{-1})	4088 ± 19972	730 ± 467	NS
PVRG (dyne-s-cm^{-5}-100gm^{-1})	116 ± 124	17 ± 14	$p<.0001$
PPP (mmHg)	15.4 ± 5.2	6.0 ± 2.7	$p<.0001$
MPP (mmHg)	48.4 ± 12.0	57.1 ± 11.3	$p<.0001$

(values presented are mean ± standard deviation)

TITLE: INTERACTION OF HYPOTHERMIA AND FENTANYL IN THE ENFLURANE ANESTHETISED DOG - DOES ACUTE TOLERANCE TO FENTANYL DEVELOP?

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Supported by the Canadian Anaesthetists' Society Research Award and Janssen Pharmaceutica.

Introduction: Our clinical observation has been that of a reduced requirement for anesthesia following separation from hypothermic cardiopulmonary bypass (CPB). The roles which the combination of hypothermia and fentanyl may play in reducing enflurane requirements following CPB is unknown. Although each separately has been shown to have an effect,(1,2) their combined effects are unknown. This study on dogs sought to determine the role that graded degrees of hypothermia in combination with a continuous infusion of fentanyl play in altering enflurane MAC.

Methods: Following institutional approval mongrel dogs (n=6) were anesthetised with enflurane (ENF) in oxygen utilising a specialised mask and a Mapleson D coaxial circuit. Monitors placed included the ECG, systemic arterial, pulmonary arterial (PA), and urinary catheters. Temperature was measured from the tip of the PA (CTEMP) and urinary catheter (CTEMP), and end-tidal ENF via a Puritan-Bennett Anesthesia Agent Monitor. MAC was determined by the tail-clamp method (1) at 36-38°C, 33-35°C, 28-30°C, and following rewarming to 33-35°C and 36-38°C. Following recovery one week later, each dog was anesthetised with ENF in oxygen as before, MAC was determined at 36-38°C, and then a fentanyl infusion (15 µg/kg over 20 min + 0.05 $\mu g.kg^{-1}.min^{-1}$) designed to reduce MAC by 30% and produce a plasma fentanyl concentration ([FEN]) of 2-4 ng/ml was initiated.(1) MAC was then redetermined at each of the temperature levels. [FEN] were determined by a RIA technique.(3) Paired t-tests and one-way ANOVA determined statistical significance ($p<0.05$).

Results: MAC did not differ between the two study periods (2.38±0.25 vs 2.23±0.30; $p<0.05$; mean ± SD). Hypothermia produced increasing degrees of MAC reduction with decreasing temperature (Table and Figure). No hysteresis was observed during rewarming. Addition of fentanyl produced the predicted degree of MAC reduction at normothermia but thereafter produced a less than additive reduction of MAC when combined with hypothermia. The predicted degree of reduction differed statistically from the actual degree of reduction beginning at 28°C and during rewarming. At the final measurement point (35-37°C during rewarming), the degree of reduction produced by fentanyl and hypothermia did not differ from that produced by hypothermia alone. [FEN] were stable throughout each measurement period (Table) and did not differ significantly between measurement periods.

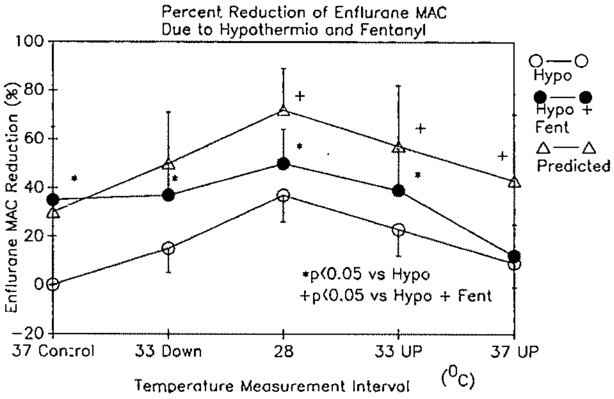

TABLE: Enflurane MAC Reduction Due to Hypothermia + Fentanyl (mean±SD)

ORDER OF STUDY	TEMP RANGE (°C)	MAC RED(%)			[FEN] (ng/ml)[4]
		HYPO[1]	HYPO+FENT[2]	PRED[3]	
1	35-37	0	35±20*	35±20	3.2±0.2
2	32-34	15±10	37±13*	50±21	3.2±0.2
3	28-30	37±11*	50±14*	72±17**	4.0±0.5
4	32-34	23±11*	39±17*	57±25**	3.5±0.2
5	35-37	9±10	12±13	43±27**	2.7±0.0

*$p<0.05$ vs value at 35-37° (control)
**$p<0.05$ vs HYPO + FENT
[1] HYPO = MAC reduction due to hypothermia alone in the indicated temperature range.
[2] HYPO+FENT = MAC reduction due to hypothermia + a constant infusion of fentanyl 0.05 $\mu g.kg^{-1}.min^{-1}$.
[3] PRED = Predicted MAC reduction determined by adding the degree of MAC reduction in each animal produced by fentanyl at normothermia to that produced at each temperature by hypothermia alone.
[4] [FEN] = Concentration of fentanyl (ng/ml) in plasma during the determination of MAC at each temperature level.

Discussion: Hypothermia + fentanyl produced a less than additive effect when combined to reduce enflurane MAC. This is unlikely to be due to alterations in the efficacy of hypothermia (not demonstrated in the control experiment). Rather, the results suggest a progressively decreasing effectiveness of fentanyl in reducing enflurane MAC in spite of stable plasma levels (possibly acute tolerance). Our clinical observation of reduced anesthetic requirements following separation from CPB cannot be explained by a synergistic interaction between fentanyl and hypothermia.

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TITLE: DOES CARDIOPULMONARY BYPASS ALTER THE REQUIREMENTS FOR ENFLURANE ANESTHESIA IN DOGS?

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Supported by the Canadian Anaesthetists' Society Research Award.

Introduction: Our clinical impression was of a reduced requirement for anesthesia following cardiopulmonary bypass (CPB) despite reduced levels of anesthetic so as to avoid myocardial depression. This study determined whether CPB alters the requirement for enflurane (ENF) anesthesia.

Methods: Following institutional approval, ten mongrel dogs weighing 19.9±3.2 kg (all results Mean ± SD) were each anesthetised with ENF in oxygen. Monitors placed included an ECG, systemic arterial, pulmonary arterial (PA), and urinary catheters. Temperature was measured from the PA (CTEMP) and urinary (UTEMP) catheters. End-tidal ENF concentration was measured by a calibrated Puritan-Bennett Anesthesia Agent Monitor. MAC was determined by the tail clamp method.(1) Arterial blood gases were measured prior to (n=10), and following separation (n=7) from CPB. Body temperature was maintained in the range of 35-37°C. Following determination of each animal's control MAC, anesthesia was deepened, heparin administered, and CPB was initiated at flows of 70-80 ml/kg with a mean systemic pressure of 50-70 mm Hg. Bubble oxygenators were employed in all cases. After 1 hr, CPB was terminated, protamine given, and MAC again determined. Group 1 (n-6) had CPB utilising aorto-atrial cannulation. Group 2 (n=4) were treated exactly as Group 1 except that femoral artery-vein cannulation was employed and hematocrit was measured pre- and post-CPB. Paired t-tests with Benferroni correction were used to determine statistical differences ($p<0.05$).

Results: Control MAC was 2.16±0.32% (n=10). For Group 1, the mean ENF MAC reduction following CPB was 30.1±21.5% ($p<0.05$; Table 1). For Group 2, the mean reduction was 19.8±8.6% (NS vs Group 1; $p<0.05$ vs Control; Fig 1). CTEMP or UTEMP pre- vs post-CPB did not differ. In Group 2 the hematocrit pre- (39.8±6.1%) vs post-CPB (31.0±4.0%) fell ($p=0.06$). MAC was determined within 1.2±0.5 hr following CPB. The hemodynamic and acid-base data for the two groups were pooled. Mean arterial pressure fell following CPB (81±14 to 67±16 mm Hg; $p<0.05$). There were no other significant hemodynamic changes. $PaCO_2$ and pH pre- vs post-CPB did not differ but the PaO_2 fell (443±43 to 386±87 mm Hg; $p<0.05$).

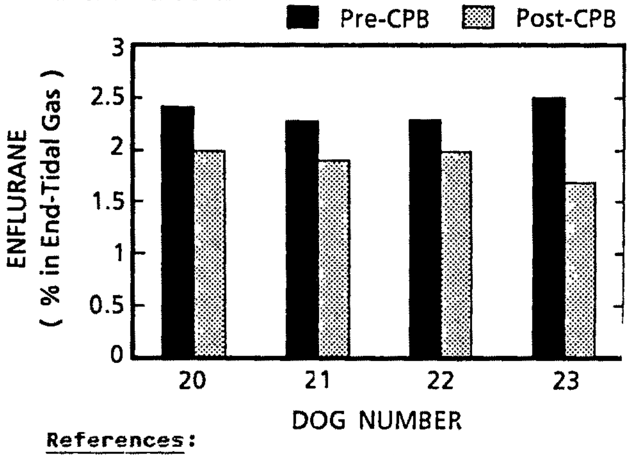
Discussion: MAC was significantly reduced following cardiopulmonary bypass (20-30%) irrespective of the cannulation technique employed. This was not due to changes in temperature or acid-base status. Hypotension occurred but the range (51-83 mm Hg) is still above the level associated with changes in MAC.(2) Anemia is unlikely to be the explanation.(3) We conclude that CPB itself reduces enflurane requirements for anesthesia by an unknown mechanism.

TABLE 1. MAC reduction due to CPB employing aorto-atrial cannulation in 6 dogs anesthetised with Enflurane.

Dog No.	Control MAC (%)	Temp (°C)	Post CPB MAC (%)	Reduction (%)	Post CPB Temp (°C)
11	1.50	34.8	0.90	40.0	34.8
12	2.10	32.3	1.62	22.9	36.4
13	2.10	37.1	2.02	3.8	36.2
15	2.33	36.6	2.10	9.9	36.4
16	2.37	38.2	1.30	45.3	35.0
18	1.70	35.8	0.70	58.8	34.9
Mean±SD	2.02±0.35	35.8±2.1	1.44±0.58*	30.1±21.5	35.6±0.6

*p<0.05 vs Control MAC

FIGURE 1. MAC determined pre- and post-CPB in 4 dogs employing femoral A-V cannulation.



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TITLE: THE EFFECT OF A BOLUS DOSE OF ESMOLOL ON THE CARDIOVASCULAR RESPONSE TO ELECTROCONVULSIVE THERAPY.

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Introduction: Esmolol is a short acting beta adrenergic blocking agent capable of obtunding the rise in heart rate associated with tracheal intubation[1]. Electroconvulsive therapy (ECT), utlizing general anesthesia, is widely used in the treatment of depressive disorders. A consequence of ECT is a transient tachycardia and systemic hypertension, due to activation of the sympathetic nervous system. This may be detrimental to patients with cardiovascular disease. Here we describe the effects of a single intravenous bolus of esmolol prior to the administration of ECT.

Methods The study had the approval of the local Human Investigation Subcommittee. All the 7 patients were adult, and gave written informed consent. Asthmatics, patients with congestive cardiac failure, heart block or taking cardiovascular medications, were excluded from the study. Monitoring included EKG, pulse oximetry and blood pressure as measured by the Dynamap 1846 SX. Initially all 7 patients received atropine 0.6mg I.V. One minute later anesthesia was induced with methohexital 1mg/kg and succinylcholine 0.5mg/kg. Then each patient on 2 separate occasions received either saline 0.9% or esmolol 1mg/kg in a blinded manner, given over 60sec. After a further 1 minute interval, ECT (140-170volts for 0.6-1sec) was administered. The current and duration of ECT was identical on each patient's 2 treatment occasions. Oxygen was administered throughout by a face mask until the return of spontaneous ventilation. Vital signs were recorded during induction and at 1 minute intervals following ECT, for a period of 10 minutes. Presence of piloerection and strength and duration of seizures were noted. A mixed design analysis of variance was utilized with a 2 level between groups factor and a 4 level repeated measures factor.

Results Mean baseline heart rate (HR) for the placebo and esmolol occasions were 82±5 SEM, B.P.M. and 74±2 SEM B.P.M. respectively. Mean baseline mean arterial pressure (MAP) for the placebo and esmolol occasions were 95± 5 SEM mmHg and 98±3 SEM mmHg respectively.

The increases in H.R. and MAP following ECT on the placebo occasions were statistically significant up to 5 minutes ($p<0.05$).

Administration of a bolus of esmolol 1mg/kg prior to ECT significantly reduced the rise in HR during the 5 minutes following administration of the current ($p <0.05$) Figure 1 shows a maximal increase from the baseline HR of 50% at 1 minute, reduced to 18% by esmolol treatment.

Although there was an increase in the MAP in the esmolol pretreated occasions up to 3 minutes after ECT it was significantly less than on the placebo occasions ($p<0.05$).

Figure 2 shows the change in mean MAP.

On no occasion was bradycardia (HR<50) nor hypotension (MAP <70% baseline), noted. No difference in the incidence of piloerection, strength and duration of seizure was noted between the esmolol and placebo occasions.

Discussion Esmolol 1mg/kg by bolus injection successfully reduced the cardiovascular changes associated with ECT. This may be of benefit to patients with cardiovascular disease where a sudden increase in myocardial oxygen demand may be harmful. The technique was also convenient to administer and did not effect other manifestations of successful ECT in these patients in the study. No ontoward effects were noted in the esmolol treatment occasions.

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FIGURE 1

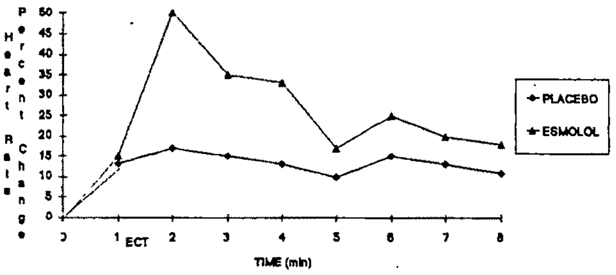
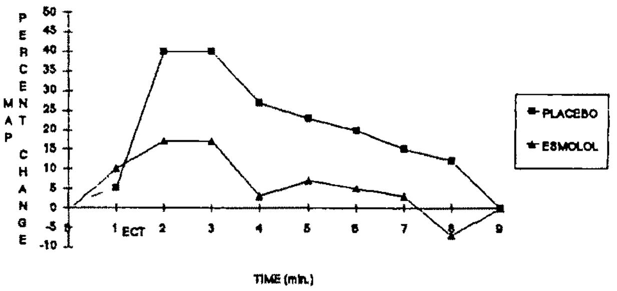


Figure 2



TITLE: INDUCTION DOSE OF PROPOFOL IN UNPREMEDICATED CHILDREN

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Propofol is a new short-acting intravenous anesthetic with high lipid solubility and short elimination half-life. The drug has been investigated extensively in Europe for anesthesia induction in adults,[1] but experience with this new agent in children is limited.

This study examines the induction characteristics and dose requirements as well as cardiovascular and respiratory effects of propofol in three age groups of unpremedicated children.

METHODS: Institutional approval and parental consent were obtained to study 90 ASA PS I or II unpremedicated 3-12 yr. old children. The patients were divided into three groups according to their age: group one 3-5 yrs, group two 6-8 yrs and group three 9-12 yrs.

To encourage participation in the study, a 24 gauge catheter was inserted by the anesthesiologist in an antecubital vein, and used for preoperative blood drawing (CBC) instead of sending the child to the lab. The catheter was then flushed with heparin solution and later used to inject the induction dose of propofol without the need for a separate venipuncture.

The children in each age group were randomized to receive one of five possible doses of propofol: 1,1.5,2,2.5 or 3 mg/kg injected over 10-30 seconds. Onset of sleep was correlated with loss of eyelash reflex within 50 sec. of propofol injection. Subsequent response to gentle application of a face mask delivering 60% N_2O and 1% halothane was judged to be excellent if it resulted in no movement, acceptable if it resulted in some movement but did not necessitate removing the mask, or unacceptable if the child moved excessively or pushed the mask away. A successful induction was defined by loss of eyelash reflex within 50 seconds, followed by excellent or acceptable response to the face mask. Changes in heart rate, blood pressure, respiration and SpO_2 were recorded by an independent observer every minute for the first 10 min. and every 10 min. thereafter until the end of surgery. The injection site was examined 24 hrs. later for possible phlebitis, irritation or thrombosis.

RESULTS: The dose of propofol (mg/kg) that resulted in loss of eyelash reflex as well as the dose that resulted in a successful induction (including mask acceptance) in 50% (ED_{50}) and 95% (ED_{95}) of patients (with 95% confidence interval) is shown in table 1. There was no statistically significant difference in the ED_{50} or ED_{95} of propofol among the three age groups.

Involuntary or semipurposeful movements were observed in 12.7% of patients who had succesful inductions. Six patients (6.6%) complained of mild to moderate pain during injection of propofol. No evidence of any venous sequelae at the injection site was seen. Apnea of greater than 20 second duration occurred in 25% of patients who received propofol in a dose of 2 mg/kg or higher. Assisted ventilation was instituted until spontaneous respiration resumed.

Table 1: Estimated dose of propofol (mg/kg) that induced anesthesia in 50% and 95% of patients with 95% confidence intervals.

Response	ED_{50}	ED_{95}
Loss of eyelash reflex (sleep)	1.27 (1.11-1.42)	1.97 (1.71-2.61)
Successful induction (sleep + mask acceptance)	1.50 (1.33-1.67)	2.34 (2.06-2.95)

Forty-eight percent of the patients had a 20% or more drop in blood pressure 1-10 minutes after propofol administration at the same time as halothane (1-3%) was introduced. 68.8% of the hypotensive episodes began 4 minutes of later after the end or the bolus injection.

DISCUSSION: Anesthesiologists continue to search for an intravenous induction agent that produces rapid onset of anesthesia and quick recovery. The results of this study indicate that propofol is an effective induction agent in young unpremedicated children. A dose range of 2.5-3.0 mg/kg is recommended to induce sleep and assure smooth acceptance of subsequent mask application. This dose is considerably less than that recommended by a recent British study[2]. The difference may be explained in part by the fact that we allowed up to 50 sec. to determine the adequacy of the induction dose vs. 20 sec. in their paper.[2]

The incidence of pain on injection, which has been reported to be as high as 44% when hand veins are used[3], was infrequently seen (< 7%) in our patients who had the drug injected into the large anticubital veins. The decrease in systolic blood pressure when propofol induction was followed by halothane was well tolerated by healthy patients and required no more intervention than reducing the halothane concentration.

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TITLE: PRESSURE SUPPORT VENTILATION PROVIDES EFFECTIVE VENTILATION DURING GENERAL ANESTHESIA FOR ELECTIVE ORTHOPEDIC SURGERY

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INTRODUCTION: Pressure support ventilation as a modality for intensive care patients is well described (1, 2). We are not aware of prior descriptions of pressure support ventilation as the sole means of ventilation during general anesthesia. We describe our implementation of this mode of ventilation in human subjects undergoing elective surgery of the upper and lower extremities.

METHODS: Ten male ASA I and ASA II patients scheduled for elective surgery of the upper or lower extremities were chosen for evaluation of the efficacy of pressure support ventilation. Informed consent and human subject committee approval were obtained. Preoperative pulmonary functions were obtained within 12 hours of surgery. All patients were induced with thiopental 5 mg/kg intravenously after sedation with fentanyl 1.5 μg/kg and midazolam 0.15 mg/kg. Orotracheal intubation was performed after neuromuscular relaxation with succinylcholine 1.0 mg/kg. Pressure support ventilation was performed with the Siemens 900C ventilator adapted for administration of inhalational anesthetics. Intermittent mandatory ventilation was utilized until the first return of motor activity detected by a standard peripheral nerve stimulator placed over the ulnar nerve distribution. Patients were then administered pressure support ventilation adjusted to a pressure yielding a tidal volume within the range of 12-15 cc/kg. Maintenance anesthesia administered was isoflurane and nitrous oxide in oxygen. Oxygen saturation was measured with a pulse oximeter, BP with an automated blood pressure cuff, heart rate with standard electrocardiogram, end tidal anesthetic concentration and carbon dioxide tension with a mass spectrometer. Patients were extubated in the operating room after completion of surgery and taken to the anesthetic recovery room. Postoperative pulmonary functions were obtained within 24 hours of surgery. Percent change in forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), and forced expiratory volume between 25 percent and 50 percent of forced vital capacity (FEV25-75) were determined.

RESULTS: All patients were effectively ventilated with pressure support once motor activity returned as judged by peripheral nerve stimulation. Demographic data and parameters during ventilation are given in Table 1. Pressure support required for ventilation ranged from 10 to 28 cm H_2O. Mean pressure support was 16 (S.D. 4) cm H_2O. Oxygen saturation during administration of 30 to 50 percent oxygen ranged from 95 to 98 percent. The lowest mean oxygen saturation of the group studied was 97 (S.D 1) percent. Peak end tidal carbon dioxide concentrations ranged from 32 to 56 mm Hg. The mean peak end tidal carbon dioxide tension was 47 (S.D. 6) mm Hg. No patients developed hypotension. Hypertension was infrequent and managed with additional intravenous administration of fentanyl or increased inspired concentration of isoflurane. Episodes of light anesthesia characterized by tachycardia, rise in blood pressure, or motor activity were preceded by a rise in respiratory rate which prompted additional anesthetic administration as noted. Percentage change in pulmonary functions before and after pressure support ventilation are given in Table 2. These percentage changes were not statistically significant.

DISCUSSION: We have demonstrated that the intraoperative use of pressure support ventilation maintains satisfactory oxygenation and sustains a sufficient minute ventilation. The extent to which the physiology of preserved spontaneous diaphragmatic activity alters the intraoperative course or postoperative recovery are yet to be fully understood. Pulmonary function tests, however, reveal no marked impairment of the mechanics of ventilation as a result of intraoperative pressure support ventilation. We conclude that pressure support ventilation is an effective means of ventilation during general anesthesia.

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TABLE 1

Parameters	Mean Value	S.D.
Age (years)	33	11
Duration of anesthesia (min.)	155	72
Peak $ETCO_2$ (mm Hg)	47	6
SaO_2 (%)	97	1
Pressure Support (cm H_2O)	16	4

TABLE 2
Percent Change in Pulmonary Function from
Baseline after Pressure Support

Patient Number	FVC	FEV1	PEFR	FEF25-75
1	-10	-6	-18	4
2	9	8	28	5
3	0	-5	2	-13
4	-4	-1	6	9
5	-13	-4	10	8
5	15	16	-23	23
7	-9	-11	7	-16
3	0	-1	-6	-3
9	-4	-3	10	-2
10	-3	-3	-21	1
Mean	-1.9	-1.0	-0.5	1.6
S.D.	8.1	7.2	15.5	10.6

Title: CEREBRAL CORTICAL OXYGENATION ASSESSED BY REFLECTANCE INFRARED PULSE OXIMETRY IN YUCATAN MINIPIGS

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Introduction. The brain, more than any other organ, is critically dependent on the maintenance of continuous blood flow. Irreversible neuronal damage may occur in as little as 4 minutes following complete ischemia/anoxia (1). Clinical assessment of cerebral blood flow is technically difficult and the use of currently available techniques are expensive and do not allow for real-time continuous monitoring. We have recently employed a reflectance infrared pulse oximetric probe to monitor cortical hemoglobin oxygen saturation to assess cerebral oxygenation *in vivo*.

Methods. With permission from our institutional animal care and use committee, eight sexually mature Yucatan minipigs weighing 14.0 to 16.0 kilograms were premedicated with ketamine and xylazine. Anesthesia was induced and maintained with isoflurane (1.6 - 2.2 %) in an air/oxygen mixture. A femoral artery and vein were cannulated for continuous blood pressure monitoring and intravenous access. Bilateral ventricular catheters were placed to monitor intracranial pressure (ICP). The sagittal sinus was cannulated for pressure monitoring and venous blood gas sampling. A 14 mm frontal burr hole was made to expose the dura over the right frontal cortex and a combined red/infrared light emitting diode and photodetector was placed epidurally under the adjacent skull. This probe was connected to a signal demodulator to determine the signal ratio of reflected light at 660 and 940 nm wavelengths. The signal demodulator calculated the percent oxygen saturation of hemoglobin of the illuminated cortex. Animals were then subjected to graded hypoxia acute hyperventilation and elevated ICP. Cortical oximetric recordings, end tidal CO_2, arterial blood pressure, ICP, expired oxygen concentration, and inspired anesthetic concentration were continuously monitored. Arterial and sagittal sinus blood samples were drawn intermittently for blood gas analysis and calculation of arterial-venous oxygen (AV O_2) differences.

Results. Cortical oximetry correlated well with expired oxygen concentration (figure 1 below) as well as with PaO_2, O_2 saturation and total O_2 content and AV O_2 differences. Decreases in cortical oximetric values paralleled decreases in arterial pO_2, arterial O_2 saturation and sagittal sinus pO_2 during experimental hypoxia (a representative time-course tracing in figure 2 below). In addition, cortical oximetry desaturation corresponded well to elevations in ICP and acute hyperventilation.

Discussion. This data suggests that reflectance cortical oximetry may be a suitable method to assess, in real time, the adequacy of cerebral perfusion both experimentally and in clinical situations.

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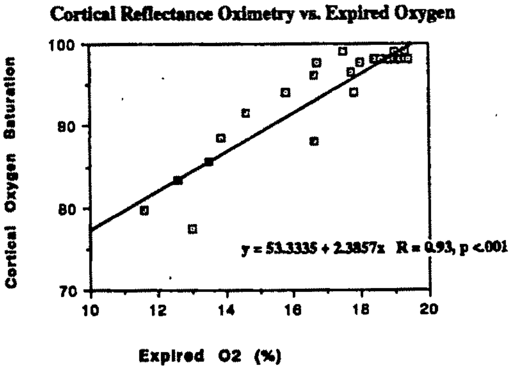

Figure 1

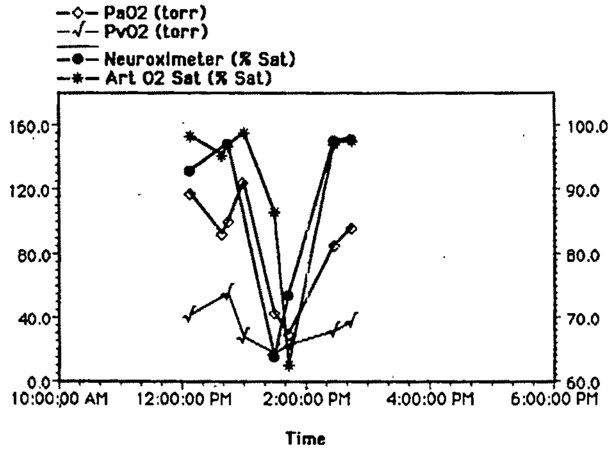

Figure 2

Title: EFFECT OF CONCENTRATION OF EPINEPHRINE IN 1% LIDOCAINE ON SKIN BLOOD FLOW IN HUMANS

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Introduction: In clinically useful concentrations, lidocaine has been shown to produce significant vasodilation[1]. Epinephrine is frequently added to local anesthetics to decrease bleeding and decrease anesthetic uptake, thereby prolonging duration of action and decreasing systemic blood levels.

The optimal concentration of epinephrine needed to counteract this vasodilatory effect is controversial. Evaluations of the effectiveness of epinephrine for this purpose have frequently relied on indirect methods and animal studies[2]. The laser Doppler is a useful tool for accurately following dynamic changes in tissue perfusion[3].

This study attempts to define the minimal concentration of epinephrine necessary to counteract the vasodilatory effect of 1% lidocaine.

Methods: After written informed consent and institutional approval, 6 healthy adult volunteers were studied. Monitors included continuous ECG, intermittent blood pressure (determined at the calf), and forearm skin temperature.

8 sites, at least 5 cm apart, were marked on the forearms. Baseline flow measurements were made at each site using a laser Doppler skin blood flow monitor (Medpacific LD5000). Subcutaneous injections of 0.5 ml of test solution (lidocaine 1% without epinephrine, lidocaine 1% with epinephrine 1:50k, 1:100k, 1:200k, 1:400k, 1:800k, and 1:1,600k) were made at 7 sites. The remaining control site was not injected.

Mean blood flow measurements and vital sign assessments were made at 5, 10, 15, 20, 30, 45, and 60 minutes.

Results: As expected, subcutaneous injections of 1% lidocaine without epinephrine resulted in an increase (2-3X baseline) in skin blood flow which rapidly peaked and gradually returned to baseline within 60 minutes.

Differences in effects of solutions were assessed by ANOVA. All local anesthetic solutions containing epinephrine were effective ($p<0.05$ when compared to plain lidocaine) in preventing the vasodilation secondary to 1% lidocaine except the 1:800k solution as determined at 5 minutes ($p<0.08$). There was no significant difference between the magnitudes of vasoconstriction produced by the various concentrations of epinephrine tested.

Discussion: The vasoconstriction produced by epinephrine makes it a valuable adjuvant for use with local anesthetics. However, the use of epinephrine is associated with the risk of cardiovascular toxicity, and may also cause delayed wound healing, increased infection rates, and loss of skin flaps. It is therefore desirable to determine a minimal effective concentration of epinephrine that will prevent vasodilation.

Data are unclear regarding the optimal concentration of epinephrine to be used with local anesthetics for subcutaneous or other regional use (e.g. recent data indicate that the minimal effective epinephrine concentration may be 1:600k or less for epidural administration[4]). Our data support the suggestion that an optimal epinephrine concentration for lidocaine may be much lower than those usually clinically employed. However, epinephrine 1:800k was ineffective in preventing the vasodilation seen at 5 minutes and both the 1:800k and 1:1,600k concentrations were less reliable in their ability to prevent this vasodilation at 5 and 10 minutes (as shown by the larger standard errors). These data indicate that the optimal concentration for epinephrine in 1% lidocaine for subcutaneous administration is more than 1:800k.

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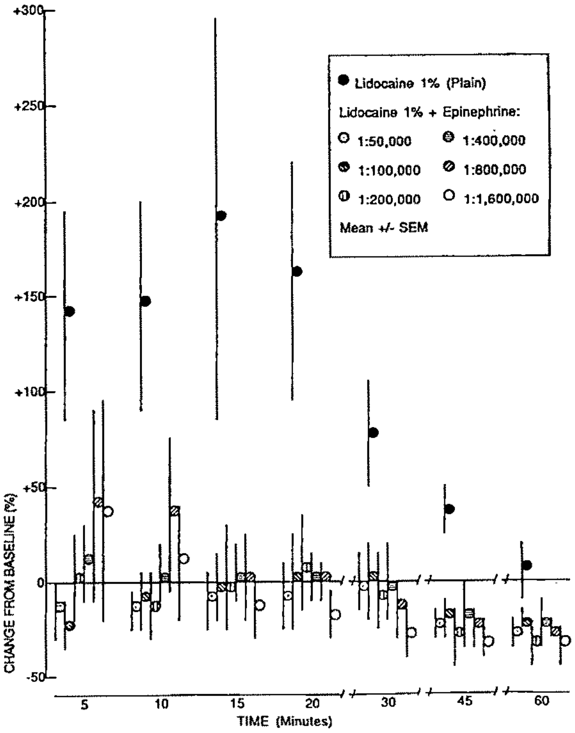
Fig.1



TITLE:
THE INFLUENCE OF ORAL FLUIDS IN POSTOPERATIVE EMESIS IN PEDIATRIC STRABISMUS SURGERY

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INTRODUCTION: Postoperative nausea and vomiting occur in up to 85% of pediatric eye surgery patients. This is not only unpleasant but can prevent discharge from a same-day surgery unit. Perioperative intravenous droperidol (75 mcg/kg) is an effective antiemetic in this group of patients, particularly when administered prior to manipulation of the eye muscles. However, these higher doses of droperidol are associated with a prolonged recovery time. Use of lower dose droperidol (25-50 mcg/kg) is a less effective antiemetic but is associated with a shorter recovery stay.

At Children's Medical Center (CMC) we have observed the incidence of postoperative emesis in this group of patients to be less than 20% despite the use of low dose droperidol. We therefore conducted a retrospective analysis of all patients having undergone strabismus surgery in the calendar year 1988 to determine the influence of anesthetic techniques including perioperative fluid administration.

METHODS: The charts of 513 patients were reviewed. Institutional Review Board approval was not required. Patients with cerebral palsy and patients receiving any antiemetic in lieu of or in addition to droperidol were excluded. 334 patients were ASA Class I, 46 were ASA Class II, and 10 were ASA Class III; 173 were females and 217 were males. The average age was 3.62 years and average weight was 17.36 kg.

No children were premedicated. Anesthesia was induced with halothane, nitrous oxide, and oxygen. All children received a nondepolarizing muscle relaxant and were ventilated with isoflurane, nitrous oxide, and oxygen. Record was made of administration of anticholinergics, narcotics, droperidol, the use of an orogastric tube, total intravenous and oral fluids received, total recovery time until discharge from hospital, and the occurrence of retching or vomiting within that time. 89% of the parents were successfully contacted the following day regarding further occurrences.

RESULTS: 390 patients received an average of 24.5 ml/kg IV fluid (14.5 ml/kg in the operating room and 10.0 ml/kg in recovery room). Average time from leaving the OR to discharge was 1.66 hours. Overall, 18.5% of patients experienced at least one episode of emesis prior to discharge. None required readmission for IV fluid hydration.

In order to ascertain which factors were predictive of emesis, contingency table analyses were performed on each factor specifically. In addition, log-linear modeling was used to compare the combined effect of pairs of factors. This showed that neither the use of an orogastric tube (to evacuate stomach contents) nor the administration of such medications as anticholinergics, opiates (fentanyl 1-2 mcg/kg or morphine 0.1 mg/kg), or droperidol (25-50 mcg/kg) had any influence on the rate of emesis. Only those patients who did not receive any oral fluids showed a significantly lower rate of emesis (Chi square 15.185, p less than 0.001). Compared individually with all other variables including opiates, droperidol, and the use of an orogastric tube, only the lack of oral fluids remained significant.

In the prediction of emesis at home, the only significant association was a prior history of emesis during recovery (Chi square 9.738, p = 0.002).

TABLE - In-Hospital Emesis

	Emesis	No Emesis	
Received oral fluids	59 24.5%	182 75.5%	241 61.8%
Received no oral fluids	18 8.7%	136 91.3%	149 38.2%
	72 18.5%	318 81.5%	390 100.0%

DISCUSSION: The etiology of emesis is complex and contributory factors include pain, narcotics, and the use of an orogastric tube. Woelfel recently investigated the contribution of dehydration and concluded that perioperative fluid replacement has no influence. The relationship between postoperative pain and nausea is well established. Controversy surrounds the use of opioid analgesics in outpatient surgery where delayed recovery and increased emesis are problems. Gastric decompression with an orogastric tube has been associated with decreased emesis. However, our study did not show this association. High dose droperidol has been shown effective in reducing emesis. Unfortunately use is associated with recovery stays of up to six hours. Lower doses given patients in this review might explain the shorter recovery times but not the lower incidence of emesis. This study shows a correlation between not-drinking and decreased emesis, which suggests that alteration of discharge criteria to eliminate the requirement of oral fluid tolerance could shorten time to discharge by decreasing incidence of emesis.

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TITLE: COLLATERAL FLOW IN A CHRONIC CANINE MULTIVESSEL CORONARY ARTERY DISEASE MODEL: EFFECT OF ISOFLURANE

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Introduction: Previous investigations[1,2] have demonstrated that vasodilator-induced redistribution of coronary collateral perfusion from ischemic to normal regions ("coronary steal") is best observed in a model which includes a total occlusion of one coronary artery and a stenosis of the artery of origin of the collateral vessels. Therefore, in the present study, the action of isoflurane on coronary perfusion distal to a total occlusion (left anterior descending; LAD) and stenosis (left circumflex; LCCA) of two coronary arteries was investigated in chronically instrumented dogs. The effects of isoflurane (2 and 3%) were assessed with and without blood pressure adjusted to conscious control levels.

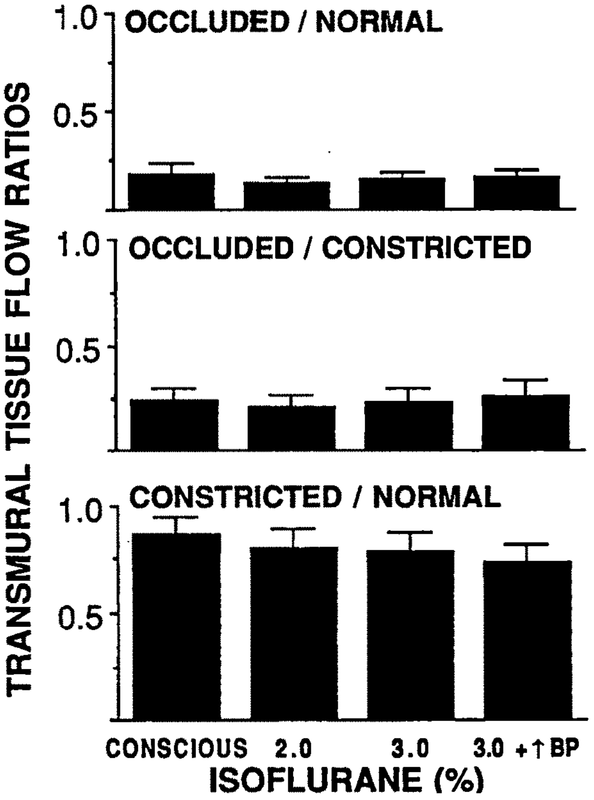
Methods: After Institutional Animal Care Committee Approval, dogs (N=9) were anesthetized and chronically instrumented for determination of myocardial blood flow (radioactive microspheres) and measurement of phasic aortic blood pressure. Doppler flow transducers were implanted on both the LAD and LCCA. In addition, a hydraulic occluder and Ameroid constrictor were placed distal to LAD and LCCA flow probes, respectively, to produce total LAD occlusion and chronic LCCA stenosis. The Ameroid produced a gradual, progressive coronary stenosis over a 1-4 week period. A left ventricular micromanometer was implanted to measure left ventricular pressure and peak +dP/dt. Ultrasonic segment length transducers were secured in the left ventricular subendocardium to evaluate regional contractility in both LAD and LCCA zones. After surgery, LAD and LCCA flow responses following left atrial injection of adenosine (100 µg bolus) were assessed daily to monitor the progression of LCCA stenosis development. When the peak LCCA vasodilator response to adenosine was attenuated by at least 75% (postoperative day 7± 1, Mean±SEM) without change in LAD coronary reserve, the effects of isoflurane on hemodynamics and regional myocardial blood flow were assessed. The LAD was totally occluded and measurements were made during the conscious state, following isoflurane (2 and 3%) and at 3% isoflurane with blood pressure adjusted to conscious levels via insertion and subsequent inflation of an aortic balloon catheter (↑ BP). Results were compared via ANOVA followed by Fishers LSD test and considered significant (*) when $p<0.05$.

Results: Isoflurane significantly reduced mean arterial pressure (2% = -28 mmHg; 3% = -38 mmHg) without change in heart rate. Peak +dP/dt and LCCA diastolic coronary vascular resistance were also decreased in a concentration dependent manner. Isoflurane reduced regional contractile function in the constricted LCCA zone. Aneurysmal bulging of the occluded LAD zone was unchanged. Isoflurane decreased myocardial blood flow in normal, constricted and occluded regions (Table). Blood flow in all regions returned to control when arterial pressure was adjusted to levels present in the conscious state. Ratios of transmural myocardial perfusion between occluded and normal or occluded and constricted regions were unchanged during isoflurane anesthesia (Figure) indicating absence of any preferential redistribution of coronary collateral perfusion.

TRANSMURAL MYOCARDIAL BLOOD FLOW (ml/min/g)

	NORMAL REGION	CONSTRICTED REGION	OCCLUDED REGION
CONSCIOUS	1.59 ± 0.12	1.40 ± 0.17	0.27 ± 0.06
2% ISOFLURANE	1.08 ± 0.08*	0.85 ± 0.11*	0.14 ± 0.04*
3% ISOFLURANE	0.88 ± 0.09*	0.69 ± 0.10*	0.12 ± 0.03*
3% ISOFLURANE + ↑ BP	1.52 ± 0.11	1.16 ± 0.18	0.23 ± 0.07

Discussion: The results of this study indicate that isoflurane does not redistribute myocardial blood flow between normal, constricted and occluded myocardium in a canine model of multivessel coronary artery disease. Reductions in myocardial blood flow during isoflurane anesthesia are dependent on systemic arterial pressure. The data demonstrates that when hypotension is corrected during isoflurane anesthesia, flow is maintained at conscious levels within regions distal to a stenosis or total occlusion, and isoflurane does not cause "coronary steal".



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Title: ARTERIOVENOUS POTASSIUM ION DIFFERENCE IN CRITICALLY ILL PATIENTS

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Introduction. In respiratory alkalosis plasma potassium concentration ([K+]) has been reported to decrease 0.6 mEq/L for each 0.1 unit change in pH because of movement of potassium ions intracellularly (1). Arterial pH is normally 0.05 to 0.08 units higher than venous pH. If intracellular potassium shifts occurred because of this pH change, there should be a 0.3 to 0.4 mEq/L difference between arterial and venous [K+]. This would be of clinical importance in diagnosing hyper- or hypokalemia, especially in the intensive care setting where patients often have blood drawn from indwelling arterial catheters. In an *in vitro* study, Kilburn equilibrated blood with low and high PCO2 and found a 0.2 mEq/L decrease in [K+] with a 0.4 unit pH increase. The objectives of the present study were to determine if venous [K+] is higher than arterial [K+] and then to examine the *in vivo* relationship between the arteriovenous pH and [K+] differences.

Methods. With the approval of the Committee of Human Research, measurements were made of [K+], blood pH, PCO2 and PO2 in simultaneous samples of arterial and peripheral venous blood in 9 critically ill patients in the ICU. To obtain a greater pH difference, simultaneous blood samples were drawn through indwelling catheters in the radial artery and internal jugular vein already in place for clinical monitoring from an additional group of 9 critically ill patients. Peripheral venous blood was drawn atraumatically from the basilic vein. Clinical laboratory analysis was within 45 minutes of sampling. [K+] was determined in an internal standard flame photometer (Instrumentation Laboratories) and pH, PCO2 and PO2 were measured with a Radiometer blood gas meter. Both instruments were calibrated with standard samples whose values bracketed the values of the experimental samples. As a control for possible changes in the blood after being drawn but before measurement, serial measurements of pH were made immediately after sampling and every 20 minutes thereafter in two samples. There was no change in pH in blood stored in either the plastic syringes or in glass heparin tubes over one hour. The paired t test was used for comparison of the arterial and venous [K+] values and the relationship between arteriovenous [K+] and pH difference was analyzed by linear regression.

Results. The data (mean ±sd) for [K+] and pH values for the peripheral and central venous versus arterial blood groups are listed in the table.

	pH		[K+]	
	arterial	venous	arterial	venous
peripheral	7.44±.09	7.40±.09	4.0±.3	4.1±.4
central	7.44±.06	7.39±.06	3.7±.5	3.8±.5

The mean difference between venous and arterial [K+] was .08 mEq/L (p=ns). Venous [K+] exceeded arterial [K+] in 7 of 19 paired samples and was less in only 1. The figure shows that there was no relationship between the arteriovenous pH and [K+] differences. Open symbols represent the peripheral venous group, closed the central venous.

Discussion. In Kilburn's *in vitro* study the change in [K+] per change in pH was about the same as in this study. Kilburn felt her data was explained by pH dependent fluid shifts across the erythrocyte membrane (diluting or concentrating plasma K+) and not by movement of potassium ions in or out of the red cell. pH dependent potassium ion shifts are known to occur in muscle cells (3) but have not been investigated in erythrocytes. Another explanation for the absence of an arteriovenous [K+] difference is that the normal erythrocyte capillary transit time might be too short to allow much potassium ion movement. In response to acute respiratory changes in pH, [K+] changes at a rate of about 0.1 mEq/L/hr (4). In either case simultaneously sampled venous and arterial [K+] are not significantly different in critically ill patients.

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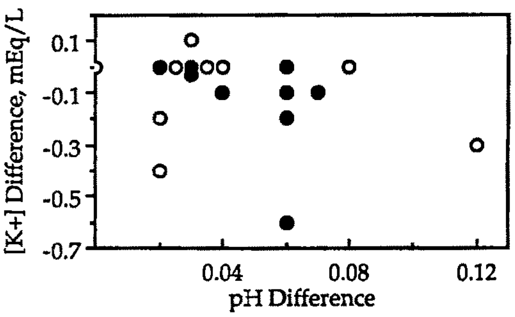

TITLE: THE ASSOCIATION OF EPIDURAL ANALGESIA AND FORCEPS DELIVERY

AUTHORS: J. L. Hawkins, M.D., B. S. Skjonsby, R.N., T. H. Joyce, III, M.D.,
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Introduction. Whether or not epidural analgesia increases the incidence of forceps delivery remains controversial. Naulty and Bailey independently reported that an increase in the use of epidurals during labor did not increase the incidence of forceps deliveries (1,2). In contrast, there are multiple reports in the obstetrical literature supporting the position that the use of epidural analgesia increases the incidence of instrumental births (3). The present study, a retrospective analysis of a representative sample of 78,387 deliveries at this institution, was undertaken to clarify this issue.

Methods. With IRB approval, the records of a total of 14,804 deliveries occurring during May, July and December of 1979-80 and 1983-85 were examined for delivery type, parity and the use of epidural analgesia. These months were selected to reflect varying levels of experience among the obstetrical housestaff. The years were selected to reflect periods prior to and following the addition of an active obstetrical anesthesia service. The data were cross-tabulated and odds-ratios (OR) and confidence intervals (95% CI) calculated. The data were compared statistically using Pearson's chi-squared test and $p<0.05$ considered significant.

Results. The percentage of patients receiving epidural analgesia increased from 3 to 27% and the incidence of forceps increased from 10 to 13% between the two time periods. Although the incidence of forceps did not increase greatly over the time periods studied, the percentage done under epidural versus other types of anesthesia (spinal or local) significantly increased from 15 to 71%.

The table compares the incidences of forceps deliveries in epidural vs non-epidural labors, and the odds-ratios and confidence intervals for the epidural/forceps association.

	EPIDURAL		NON-EPIDURAL		EPIDURAL/FORCEPS
TIME	TOTAL	FORCEPS	TOTAL	FORCEPS	OR [95% CI]
'79-80	197	81(41%)	5620	474(8%)	7.58 [5.62,10.22]
'83-85	2466	801(32%)	6521	324(5%)	9.20 [8.00,10.58]

In addition, the epidural/forceps association was even stronger for multiparous women than for primiparous women (OR 9.74 [8.26, 11.48] vs 4.52 [3.91, 5.24]). Each of the odds for forceps delivery for patients receiving epidural analgesia was significantly different from patients who did not receive an epidural($p<0.0001$).

Conclusions. This historical cohort study demonstrates a strong association between epidural analgesia for labor and instrumental delivery. Unexpectedly, this association is especially strong for multiparous mothers. These results do not imply causation, since many factors other than the anesthetic influence the obstetrical decision to use forceps.

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TITLE: IS EPIDURAL ANALGESIA THE ONLY VARIABLE ASSOCIATED WITH FORCEPS DELIVERY?

AUTHORS: J. L. Hawkins, M.D., B. S. Skjonsby, R.N., M. Kubicek, R.N., K. R. Hess, M.S., D. H. Morrow, M.D., T. H. Joyce, III, M.D.
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Introduction. Previous work by us demonstrated that use of epidural analgesia in labor is associated with an increase in instrumental deliveries. The epidural-forceps association was even stronger in multiparous patients. The present case-control study was undertaken to analyze factors, in addition to epidural anesthesia, which may be associated with an increase in the use of forceps.

Methods. With IRB approval, 20 maternal, neonatal, anesthetic, and obstetric variables were evaluated in 609 patients undergoing an instrumental delivery. Control data was collected by retrospective review of the charts of 246 patients who had a spontaneous vaginal delivery selected at random from the delivery log. The data were cross-tabulated and odds-ratios (OR) and confidence intervals (95% CI) calculated. The data were compared statistically using Pearson's chi-squared univariate analysis, followed by multivariate analysis using stepwise logistic regression; $p < 0.05$ was considered significant.

Results. Epidural analgesia was again found to have a strong association with forceps delivery (OR 9.53, CI [6.79, 13.40], $p < 0.0001$). In multiparous patients the independent epidural-forceps association was approximately 3 times stronger than in primiparous mothers, (12.55 [5.27, 29.85] vs 4.23 [2.44, 7.33]). Other independent variables associated with forceps delivery are illustrated in the Table.

Table. Independent Variables Associated With Forceps Delivery

VARIABLE	ODDS-RATIO	95% CONFIDENCE INTERVAL
Gest. Age > 41 wks	4.90	2.28, 10.52
Malpresentation: OP	6.71	2.56, 17.59
OT	8.53	3.37, 21.58
Previous C.S.	4.96	1.79, 13.69
Second stage > 2 hr	6.22	3.66, 10.56

Conclusions. This case-control study confirms our previous conclusion that use of epidural analgesia during labor substantially increases the probability for an instrumental delivery, and that the probability is further increased by multiparity. Other variables independently associated with forceps use (regardless of the use of epidural analgesia) include: gestational age greater than 41 weeks, malpresentation of the fetal head, previous cesarean section, and duration of the second stage of labor. Prematurity did not increase forceps use. Neonatal Apgar scores were unrelated to either epidural analgesia or the use of forceps. Thus, two investigations with markedly different experimental designs (a historical cohort study of 14,804 records, and a case-control study of 855 patients) supports the conclusions that: 1) an increased use of forceps for delivery is associated with epidural analgesia during labor, and 2) the association is greater for multiparous patients.

Title: **CARDIOVASCULAR DRUGS IN MODERATE HYPOTHERMIA IN SHEEP RETAIN MORE DIRECT VASCULAR ACTIVITY IN COMPARISON TO CARDIAC EFFECTS**

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INTRODUCTION. There is considerable renewed interest in using total body hypothermia in order to protect vital organs during surgery and transplantation. However, just as in accidental hypothermia, it is often difficult to judge the cardiovascular state when hypothermia is induced and drug mediated cardiovascular support is of major concern in the absence of a heart-lung machine. This study was designed to assess the effects of dobutamine, impromidine, dopexamine and sodium nitroprusside in an experimental animal model, as data on the cardiovascular performance of emergency drugs for use in hypothermia are rarely obtainable in a controlled clinical situation.

METHODS. Experiments were carried out on six anaesthetized sheep using a standard closed chest model[1]. Institutional approval was given by the animal investigation committee. Steady state hypothermia at 29°C was induced in the animals (median weight 54.5kg) within two hours by a femoral arterio-venous shunt. 29°C is a temperature which is well tolerated without the risk of cardiac arrhythmias developing. Each animal served as its own control.

Basal anaesthesia was maintained with an infusion of midazolam ($0.18 mg \cdot kg^{-1} \cdot h^{-1}$) and buprenorphine ($5.4 \mu g \cdot kg^{-1} \cdot h^{-1}$) and at half those rates during hypothermia. Controlled ventilation with an oxygen/air mixture was performed to an alpha-stat regimen[2]. During exposure of the large blood vessels anaesthesia was supplemented by ventilating with oxygen in N_2O and 0.5% halothane. Recording of the haemodynamic data was performed with standard equipment; myocardial blood flow was measured using a coronary venous bypass system (Morawitz cannula) and blocking the left azygos vein.

Dobutamine, impromidine, dopexamine and sodium nitroprusside (SNP) were applied by continuous infusion. Each dosage was given for 3 to 4 minutes allowing haemodynamically steady states to develop before increasing it. This procedure reduced the time the animal was exposed to high drug concentrations and minimized the amount of drug applied. The medication was applied both at 29°C and 39°C body temperature.

Medication	microgramme/min				
Dobutamine	25	50	75	100	12
Impromidine	10	20	30	40	5
Dopexamine	100	200	300	400	500
Sodium Nitroprusside	80	160	240	320	400

RESULTS. Under haemodynamic control conditions a reduction of body temperature by 10°C was accompanied by a decrease in heart rate of 10% and cardiac output of 6%; aortic and pulmonary artery pressures (PAP) were maintained. Despite a dP/dt increase of 60%, myocardial oxygen consumption only increased 12%. Coronary vascular resistance was similar for both temperatures. An elevated pulmonary artery oxygen saturation reflected the decrease in total body oxygen consumption of 48%.

The catecholamines, dobutamine and dopexamine, were about 70% less effective on heart rate and aortic pressure in hypothermia than in normothermia. Dopexamine reduced peripheral vascular resistance both in hypothermia and normothermia by 20%. Pulmonary vascular resistance was also reduced to the same degree in hypothermia whilst in normothermia the effect was negligible. The 25% increase in cardiac output with dopexamine was halved in hypothermia. In normothermia concomitant myocardial oxygen consumption increased by about 50%. In hypothermia this increase was less than 10% albeit the control values were 10% higher.

Impromidine in normothermia increased heart rate by 15% and reduced PAP. In hypothermia it had no effect on heart rate and its effect on PAP was halved. However, the effects of SNP on PAP (−33%) were of a comparable magnitude in both hypo- and normothermia starting from similar haemodynamic control values.

All four drugs reduced LVEDP by approximately one third (3mmHg) in normothermia. In hypothermia this reduction was only 2mmHg except for SNP which was slightly more effective. However, SNP was the only drug, at the dosages given, to reduce cardiac output. This reaction occurred only in hypothermia. Both the inotropic drugs as well as the vasodilatory drug reduced cardiac end-systolic volume. This effect was also reduced by half in hypothermia.

DISCUSSION. The main effect of hypothermia is to reduce total body oxygen consumption. Whether myocardial oxygen consumption is actually reduced depends mainly on the depth of anaesthesia and the absence of thermoregulation. From this series of experiments it may be concluded that reflex control of the circulation is virtually absent whilst metabolic control of myocardial blood flow, for example, is intact. Direct vascular drug effects are mostly maintained while cardiac effects are reduced by more than half. Previous experiments[3] have shown that drug effects in hypothermia are not necessarily related to the Q_{10} and severe paradoxical reactions may occur with calcium and dopamine[4]. While dopamine would seem to be a natural choice for cardiovascular support in hypothermia, dopexamine appears to be the better option. It does not impair cardiac function and reduces pulmonary vascular resistance in hypothermia.

In conclusion hypothermia allows the preservation of organ function with reduced organ blood flow. However, the dose response curves for catecholamines display a shift to the right and unpredictable cardiovascular reactions require extensive monitoring.

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Title: MILD INTRAOPERATIVE HYPOTHERMIA INCREASES DURATION OF ACTION AND RECOVERY TIME OF VECURONIUM

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Introduction. In the absence of muscle relaxants, adductor pollicis (AP) temperatures below 35.2°C are associated with a reduction in AP twitch tension of 15%/°C reduction in muscle temperature, when temperature in this muscle is decreased secondary to total body cooling .[1] It is therefore reasonable to assume that the neuromuscular effects of a muscle relaxant will be significantly influenced by mild hypothermia. The aim of the present study was to compare the time course of vecuronium-induced neuromuscular blockade in normothermic with that in mildly hypothermic patients.

Methods. With Committee on Human Research approval, we studied 14 unpremedicated ASA I or II patients during nitrous oxide/isoflurane anesthesia. In 10 patients central body temperature (body°C) was maintained > 36.5°C using Bair Hugger® warming unit, airway humidification and low gas flows in the anesthesia curcuit. In the remaining 4 patients central body temperature was actively reduced to 34-34.5°C using cooling blankets and iv infusion of cold (5-10°C) lactated Ringer's solution at a rate of 1 L/h. Central body temperatures were measured by a deep esophageal temperature probe. In cooled patients, skin finger tip and lower arm temperatures were recorded using self-sticking probes, in order to detect peripheral vasoconstriction. Supramaximal stimuli of 0.2 msec duration, in a train-of-four (TOF) sequence at 2 Hz, were applied via subcutaneous needle electrodes to the ulnar nerve at the wrist. Neuromuscular blockade was assessed by measuring the mechanical evoked response of the AP muscle to the first stimulus in each train (T1). When the appropriate body temperature was achieved, vecuronium 0.1 mg/kg was administered as an iv bolus. The twitch tension recorded at the time of injection of the drug was used as control twitch height. Duration of action from injection of vecuronium until T1 returned to10% of control (Dur10) was recorded in all patients. In 5 normothermic (normo) and 2 hypothermic (hypo) patients neostigmine 40 ug/kg was administered when T1 had recovered spontaneously to 10% of control. The spontaneous (spont) or neostigmine (neo) induced recovery times from T1 = 25% to T1 = 75% (RI), and T1 = 10% to TOF ratio > 75% (TOF75), were recorded.

Results. Peripheral vasoconstriction was not observed in any patient. Vecuronium was administered at 34.3 ± 0.2°C in the hypothermic and 36.5°C in the normothermic patients. The duration of action was significantly prolonged during hypothermia (table 1). Both spontaneous recovery times were prolonged during hypothermia (table 1). Neostigmine-induced recovery time from 10% to TOF ratio >75% was also prolonged during hypothermia, while recovery index was not significantly different during hypothermia and normothermia. Due to conclusion of surgery, one of the hypothermic patients that recovered spontaneously received neostigmine at TOF ratio = 45% (time after vecuronium = 65 min).

Discussion. Our data indicate that reduced body temperature significantly prolongs the duration of action of vecuronium. The study was not designed to determine the mechanisms underlying the prolonged duration of action, but both pharmacokinetic and pharmacodynamic factors may be involved. The dose regimen of this drug should be adjusted according to the body temperature, which can be accomplished by observing the twitch response to nerve stimulation during anesthesia. Because neostigmine induced recovery time seems to be significantly longer at hypothermia than normothermia, more time must be allowed to elapse in hypothermic patients for adequate recovery to occur.

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Table 1.Duration of action (Dur10), recovery index (R.I.), and recovery time from 10% spontaneous recovery to TOF ratio > 75% (TOF75) of vecuronium during normothermia and mild hypothermia. All values are mean min ± SD.

	n	Dur10	R.I	TOF75
Hypo, spont	2	67 ± 3	54 ± 8	83 ± 25*
Normo, spont	5	29 ± 2	15 ± 5	43 ± 9
Hypo, neo	2	61 ± 3	4 ± 0	23 ± 18
Normo, neo	5	28 ± 4	2 ± 1	11 ± 4

* one patient recovered only to TOF ratio = 45%

Title: EFFECTS OF THREE BUFFER SOLUTIONS ON ACIDOSIS AND SURVIVAL IN A PORCINE MODEL OF CPR

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Introduction. Administration of buffer solutions is an accepted adjunct to ACLS (1). A variety of undesirable effects are ascribed to sodium bicarbonate. A recent approach to minimize such side effects was the development of a buffer mixture (Tribonat^R)(2). The benefits of buffer treatment with respect to the outcome of CPR are, however, controversial.
We have evaluated the impact of buffering during cardiac arrest and CPR in a porcine model. Effects on acid-base balance and short term survival were assessed, comparing sodium bicarbonate, Tribonate^R, Tris-buffer and placebo.

Methods. The protocol was approved by the State Animal Investigation Committee. 28 German landrace piglets (bw x 26kg [23-29]) were randomly allocated to four groups. After premedication (azaperone 8mg/kg i.m.) the animals were anesthetized with piritramide (induction: 1mg/kg i.v., maintenance:1,2mg/kg/h; pancuronium 0,4mg/kg/h p.inf.), intubated and normoventilated (40% O_2 in N_2O; end-tidal capnometry). Instrumentation included 2 arterial lines, a fiberoptic P.A.-catheter, a triple lumen c.v.-line and a cerebral ventricle catheter. Ventricular fibrillation was induced by AC via a pacing catheter. Following 4 min of circulatory arrest CPR was initiated by 2 ventilations followed by chest compressions (100/min.) using a Thumper^{TM} (compression/ventilation ratio 5:1; duty cycle 50%; compression force 100 N). Ventilation was controlled (20/min.) to deliver the pre-arrest volume. With the onset of CPR a bolus of epinephrine (40ìg/kg i.v.) was administered, followed by a continous infusion (20ìg/kg/min.). Infusion of the buffer was continued throughout the CPR-period of 10 min

Group	Dosage	n
Control (NaCl 0,9%)	1 ml/kg	7
$NaHCO_3$ 8,4%	1 mmol/kg	7
Tribonate^R	1 mmol/kg	7
Tris 1 m	1 mmol/kg	7

After 10 min of CPR defibrillation was attempted with 120 J. Survival was defined as the restoration of spontaneous circulation (MAP $\geq$ 50 mmHg) without further drug support. Arterial and central venous blood samples were obtained 5 min before and during arrest. Three more samples were taken during CPR and another three after defibrillation. Statistical evaluation utilized ANOVA and Fisher's Exact Test.

Results. During CPR, control animals developed a metabolic arterial acidosis; arterial pH was preserved within the prearrest range by NaHCO3 and Tribonate^R, whereas Tris caused a hypocapnic alkalosis in the arterial blood. Arterial base excess was preserved best by NaHCO3. During CPR control animals developed a pronounced combined venous acidosis. Animals buffered with NaHCO3 or Tribonate^R showed mild hypercapnic acidosis, whereas Tris caused pure hypocapnic alkalosis in the central venous circulation. The overall rate of short term survival in this model was 42 %.

Group	Short term survival	
Control	2 / 7	(29%)
$NaHCO_3$	4 / 7	(57%)
Tribonate^R	4 / 7	(57%)
Tris	1 / 7	(14%)

There was no significant difference in short term survival between the four groups.

Discussion. Ensuring adequade alveolar ventilation is the main factor in controlling acid-base disturbance under the condition of cardiac arrest. Hyperventilation corrects respiratory acidosis by removing CO_2 (1). This, however, affects the arterial blood only. On the venous side a combined acidosis is an indication for buffer therapy.
We found that buffer treatment with NaHCO3 does not affect the acid-base balance adversely with respect to effectiveness of defibrillation and outcome. Due to buffer effects, we see a shift to higher pH values. We did not see an "exaberation of central venous acidosis" by sodium bicarbonate as described by Weil et al.(3). With the restoration of spontaneous circulation, elimination of the CO_2, generated by $NaHCO_3$-buffering, does not present a problem. The suggested superiority of the new Tribonate^R over NaHCO3 could not be confirmed in this CPR-model. Tris lead to an arterial and c.v. alkalosis which adversely affected defibrillation and outcome.
We conclude, that buffering improves acid-base balance, and that bicarbonate and Tribonate^R offers certain advantages over Tris-buffer in this model.

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Title: THE EFFECT OF FENTANYL AND SUFENTANIL ON BRAIN RETRACTOR PRESSURE

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Introduction: A direct relationship has been demonstrated between brain retractor pressure (BRP) and regional cerebral dysfunction.[1] Recently, sufentanil has been shown to cause an increase in cerebrospinal fluid pressure and a decrease in cerebral perfusion pressure (CPP) in patients with cerebral tumors.[2] This study was designed to prospectively investigate the effect of sufentanil and fentanyl administration on BRP.

Methods: Following institutional ethics approval and acquisition of informed consent, sixteen adult patients undergoing craniotomy for aneurysm (12) tumour (3) or CSF leak (1) were studied in a randomized, blinded fashion. Patients received fentanyl (F) 2.0 mcg/kg (n=5), sufentanil (S) 0.4 mcg/kg (n=5) or normal saline (NS) (n=6). General anesthesia was induced with fentanyl 3.0 mcg/kg, thiopentone and succinylcholine or atracurium. Anesthesia was maintained with isoflurane in air/oxygen and atracurium. Additional boluses of thiopentone were given in response to positioning and skull pin insertion. All patients received mannitol 0.5-1.0 gm/kg prior to opening dura. The EKG, intra-arterial BP and $ETCO_2$ were monitored continuously. All patients were hyperventilated to a stable $ETCO_2$ between 25-35 mmHg. Inspired isoflurane concentrations were at 1.5% or less prior to each study. Following dural opening an Albin-Buneguin pressure sensitive brain retractor[1] was placed by the surgeon. Initial retractor pressure was established at approximately 10mmHg and all surgical activity was halted. Following 5-10 minutes for equilibration, one of the study drugs was given as an IV bolus and the response monitored for a further 10 minutes. Regional cerebral perfusion pressure was calculated as rCPP= MAP-BRP. Statistical comparisons were done using ANOVA for repeated measures and the Student-Newman-Keuls test. $p<0.05$ was regarded as significant.

Results: BRP demonstrated a progressive gentle decline in each study group (figure 1). A significant difference in BRP was found between the F and S groups at 3 and 5 minutes only. Otherwise no significant differences in BRP were found either between or within the three groups. MAP and rCPP were higher in the S group prior to drug administration (figure 1). Following drug administration both MAP and rCPP decreased in the F and S groups differing significantly from the NS group at 6 minutes and beyond.

No significant differences in MAP or rCPP were found between the F and S groups. Within groups the decline in MAP and rCPP for F and S reached significance within 2-3 minutes. Mean inspired isoflurane concentrations were similar in all groups. However, isoflurane was reduced in 2 patients in the F group and 3 patients in the S group to compensate for MAP below 60 mmHg..

Discussion: Neither of the narcotics produced a significant increase in BRP. Thus, increases in ICP attributed to sufentanil would not appear to directly influence BRP once the dura is opened. A decrease in MAP results in a decline in rCPP. This could compromise cerebral tissues underlying the retractor. Although both fentanyl and sufentanil produced significant decreases in MAP and rCPP, the. results of this study showed no significant difference between these two narcotics with regard to these effects.

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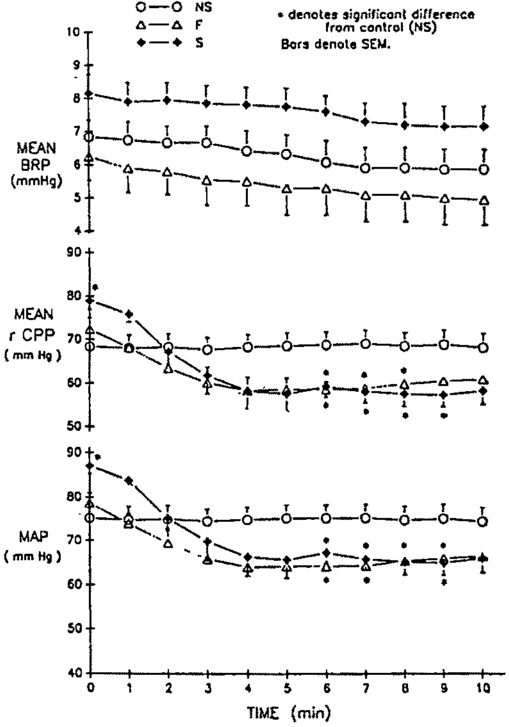
FIGURE 1



TITLE: A COMPARISON OF 0.5% BUPIVACAINE AND 0.5% ROPIVACAINE FOR BRACHIAL PLEXUS BLOCK

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Introduction: Ropivacaine is a new amide local anesthetic that has been shown in animal studies to be a potent long acting agent similar to bupivacaine but with a lower cardiotoxic potential.[1] In human brachial plexus studies, 0.5% ropivacaine both with and without epinephrine (1:200,000) has been shown to produce excellent sensory analgesia and anesthesia as well as motor block.[2] The main objective of the present study was to compare the anesthetic characteristics of 0.5% ropivacaine and 0.5% bupivacaine when used for brachial plexus block using the subclavian perivascular technique.

Methods: The Institutional Review Board provided approval prior to initiation of the study. Enrolled in this double blind randomized study were 48 ASA I or II patients scheduled to undergo upper extremity surgery under brachial plexus anesthesia. After premedication with 0.15 mg/kg of morphine sulfate IM and versed 0-3.0 mg IV, each patient received a subclavian perivascular block following elicitation of a paresthesia. Group I (n=24) received 0.5% bupivacaine and Group II (n=24) received 0.5% ropivacaine, both without epinephrine. Thirty five ml of anesthetic solution was injected for the subclavian perivascular block and 3 ml was used to block the intercostobrachial nerve in the axilla. Sensory and motor recordings were done prior to the block and at 2,5,10,15,20,25 and 30 minutes following the block, then every 15 minutes until 5 hours, then every 30 minutes until 12 hours, and then every 60 minutes until complete resolution of the block. Sensory block was graded such that 0 = no loss of sensation to pinprick, 1 = analgesia (patient feels touch but not sharp) and 2 = anesthesia (patient does not feel touch). Motor block was assessed at the shoulder and hand with 0 = no weakness, 1 = paresis, and 2 = paralysis. Data was analyzed using Fisher's exact test and unpaired student t tests, with $p<.05$ considered statistically significant.

Results: There were no significant differences between groups in terms of age, height, weight or female to male ratio. Onset times for analgesia and anesthesia in each of the C5 through T1 dermatomes were found not to differ significantly between the bupivacaine 0.5% and ropivacaine 0.5% groups (Table 1). The duration of analgesia and anesthesia was prolonged, and also did not differ significantly between groups (Table 2).

Motor block was profound with 100% of patients in both groups developing shoulder paralysis as well as hand paresis. Two patients in each group required supplemental blocks prior to surgery.

Discussion: Both bupivacaine 0.5% and ropivacaine 0.5% produced effective brachial plexus anesthesia of prolonged duration. Our clinical impression from a prior open labeled study was that ropivacaine had a faster onset of anesthesia than bupivacaine, but this was not substantiated in the present double blind comparison. Both agents produced a profound motor block of prolonged duration, which in the case of ropivacaine is in contrast to epidural anesthesia in which only a minimal motor block accompanies the sensory changes seen with 0.5% ropivacaine.[3] Although both agents appear equally effective in providing brachial plexus anesthesia, the lesser cardiotoxic potential of ropivacaine compared to bupivacaine may be an advantage in brachial plexus and other regional blocks in which the potential for intravascular injection exists.

Study supported by a grant from Astra Alab AB and performed at Audie L. Murphy Memorial Veteran's Administration Hospital and Medical Center Hospital in San Antonio, Texas.

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Table 1

Onset of Analgesia and Anesthesia (min.)

Analgesia	C_5	C_6	C_7	C_8	T_1
Bupivacaine 0.5%	15.3 ±12.4	10.0 ± 7.0	13.9 ±28.7	10.1 ±12.6	11.0 ±12.9
Ropivacaine 0.5%	14.3 ±13.5	11.5 ± 7.8	9.7 ± 9.5	10.3 ± 9.9	8.0 ± 7.1
Anesthesia					
Bupivacaine 0.5%	40.3 ±46.9	30.4 ±21.5	30.7 ±43.2	33.1 ±32.4	16.5 ±21.1
Ropivacaine 0.5%	31.3 ±22.5	32.0 ±36.6	20.3 ±13.4	20.4 ±15.0	14.6 ±12.0

Table 2

Duration of Analgesia and Anesthesia (min.)

Analgesia	C_5	C_6	C_7	C_8	T_1
Bupivacaine 0.5%	799.3 ±254.8	7[illegible].0 ±265.2	830.2 ±249.7	844.9 ±255.0	804.2 ±254.8
Ropivacaine 0.5%	787.6 ±185.4	816.5 ±184.7	801.7 ±190.6	794.9 ±205.9	746.8 ±227.4
Anesthesia					
Bupivacaine 0.5%	590.0 ±237.5	639.4 ±267.3	668.3 ±264.0	663.1 ±262.1	630.6 ±245.3
Ropivacaine 0.5%	615.9 ±222.3	639.0 ±197.8	663.8 ±168.9	683.8 ±197.2	605.4 ±186.7

Title : Alfentanil Versus Isoflurane Anesthesia for Electro-Ejaculation
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INTRODUCTION: Sexual dysfunction in males is most commonly related to impotence but failure to ejaculate may also occur. Erection is an intricate process involving the vascular peripheral and central nervous systems, with transmission primarily through the pelvic parasympathetic nerves culminating in a release of norepinephrine from the short adrenergic nerves. Ejaculation involves emission antegrade ejaculation and bladder neck closure. Afferent stimuli travel to the higher centers via the pudendal nerve. The efferent stimuli are mediated through T12 to L2 and the thoracolumbar spinal ganglia. Sympathetic fibers pass through the inferior mesenteric ganglia and form the hypogastric nerve. This sympathetic innervation is responsible for emission and closure of the bladder neck is augmented through sympathetic stimulation. The projectile release of semen from the urethra is para-sympathetically mediated. Failure of ejaculation in potent males may occur secondary to retro-peritoneal lymph node dissection necessitated by testicular neoplasm. This dysfunction may also occur following spinal cord injury and subsequent to diseases involving the nervous system such as multiple sclerosis or diabetes mellitus. Since 1948 electrical stimulation delivered via an anal probe has been used to collect semen from patients with spinal cord injuries. The first pregnancy was reported in 1975. More recently this technique has been applied to patients without neurological impairment and thus requires anesthesia. The procedure is scheduled to coincide with the respective sexual partner's fertile cycle and intrauterine insemination performed. The procedure may be scheduled repeatedly at monthly or longer intervals.

METHOD: Following approval by the institutional human investigation committee and after obtaining written informed consent from the subjects, patients scheduled for electro-ejaculation were studied. On the first, third, fifth etc. procedure each patient was randomly assigned to group A (alfentanil) or group B (isoflurane). On the second, fourth and sixth procedure the patient was assigned to the alternative group. Following application of E.K.G. leads, pulse oximeter and B.P. cuff for automatic measurement, all patients were pre-oxygenated and intravenous midazolam administered, anesthesia was induced with a sleep dose of methohexitone and maintained with intravenous alfentanil (group A) or isoflurane (group B) titrated against changes in hemodynamic parameters. Ventilation was controlled via a face mask with 30% oxygen in nitrous oxide to maintain an end tidal carbon dioxide tension of 34-40 mm. Hg. After induction of anesthesia the patient was turned in the lateral position and following anoscopy the electroejaculation probe placed in the rectum. The probe was connected to an electrical stimulator and the voltage increased until ejaculation occurred. An average of thirty stimulations up to 22 volts are applied. Blood pressure and pulse rate were recorded at two minute intervals and control, maximum and minimum values are reported. Independent investigators, unaware of the anesthetic used measured the volume of semen, the sperm count and motility. An independent observer assessed when the patient was orientated to person, time and place. Results were analyzed using student's test.

RESULTS: A total of twenty-four patients were studied during seventy-two procedures. In the study group four pregnancies were reported. One patient withdrew from the study after the second anesthetic (alfentanil) because of nausea and a fifth pregnancy resulted from the third harvest of semen. A total of thirteen patients complained of nausea and/or vomiting following fifteen anesthetics. One patient had nausea and vomiting following exposure to both anesthetics, one had nausea following isoflurane, of the remaining eleven, two vomited following one alfentanil exposure and the remainder were nauseated following alfentanil, one patient being nauseated following two exposures. The mean total dose of alfentanil used was 70 ± 15 mg./kg. There was no significant difference between the groups as regards the dose of midazolam or methohexitone, or the length of the procedure but there was a significant difference between the two groups as regards recovery time (table 1).There was no significant difference in blood pressure between the groups but there was a significant difference in maximal and minimal pulse rates.

	B.P. mm Hg. Mean ± S.D.			Pulse Rate (B/min) Mean ± S.D.		
	Control	Max.	Min.	Control	Max.	Min.
Group A	85±15	108±18	63±12	74±12	*88±30	*64±13
Group B	90±15	114±18	73±13	79±14	120±31	86±14

* P <.01

Mean ± S.D.

	Group A	Group B
Length of Procedure (min)	18±4*	20±4
Elasped time to recovery (min)	20±16	33±17
Midazolam (mg lkg)	.04±.01	.04±.01
Methohexitone (mg. lkg)	1.2±.3	1.6±.5

* P <.01

Discussion: Alfentanil attenuated the tachy cardic response to stimulation. Although the incidence of nausea was higher in the alfentanil group this was unacceptable to only one patient. The objective of this procedure is a sucessful pregnancy; three pregnancies occurred after havesting sperm under isoflunane anesthesia and two after alfentanil, however a much larger series will be required to ascertain if the anesthetic has a result on outcome.

Title: ESOPHAGEAL DOPPLER ULTRASOUND CAN BE USED TO DETERMINE SYSTEMIC VASCULAR RESISTANCE

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Introduction: Continuous-wave esophageal Doppler ultrasound has been used to determine cardiac output (D-CO) non-invasively in man. Currently, systemic vascular resistance (SVR) is derived almost exclusively from parameters measured by invasive means: thermodilution cardiac output (T-CO), mean arterial pressure (MAP) and central venous pressure (CVP). The aim of this investigation was to assess the usefulness of non-invasively derived D-CO in the determination of SVR in anesthetized patients. This was accomplished (1) by determining SVR values from D-CO (D-SVR) and comparing them with conventional SVR, derived from T-CO in the same patients, at the same time, and (2) by determining how closely changes in D-SVR reflect the changes in conventional SVR which occur during periods of increased patient stimulation, sternotomy or surgical dissection of the left internal mammary artery in CABG patients.

Methods: 22 patients free of aortic disease undergoing CABG surgery were studied in the pre-bypass period (prior institutional IRB approval of the research protocol and written informed consent were obtained). Anesthesia consisted of fentanyl, diazepam, pancuronium and oxygen. MAP was read directly from a Hewlett-Packard 78205B monitor interfaced to a Statham P23 pressure transducer connected with a fluid-filled tubing to a radial artery cannula. Paired sets of T-CO and D-CO measurements were obtained at nearly the same instant. T-CO was determined using an American Edwards 7.5F Swan-Ganz® catheter and corresponding computer. T-CO was the average of 3 values (within 10% of each other) obtained by injecting 10 ML of room-temperature 5% dextrose solution. CVP was determined with the same catheter. Conventional SVR was calculated as: 80 x (MAP - CVP)/T-CO. D-SVR was derived from Doppler D-CO values determined with an Accucom 2® cardiac output monitor (Datascope, Paramus, NJ) and the same MAP and CVP values as used to calculate T-CO. After manual input of MAP and CVP values, the Accucom 2 automatically derives D-SVR = 80 x (MAP - CVP)/D-CO. Measurements were obtained during 2 periods: (A) after induction of anesthesia during a period of no stimulation (baseline), and (B) immediately after sternotomy or after start of the mammary artery dissection (stimulation). Results are reported as mean ± standard deviation. Statistical significance of the differences in the multiple paired comparisons was determined using the Bonferroni *t*-test with a $p < .05$ cutoff .

Results: Average values for the 22 patients are presented in the Table. Baseline D-SVR values were 1352 ± 440 dynes-sec-CM^{-5} (U) not significantly different from the corresponding conventional SVR values 1263 ± the 374 U ($p = .4$). During the stimulation period, mean D-SVR increased to 1959 ± 955 U exceeding the conventional SVR mean of 1516 ± 538 U, but the difference between the two just failed to reach significance ($p = .06$). For both Doppler and the conventional techniques, the differences in resistance values between baseline and stimulation periods were highly significant statistically ($p < .01$). Changes in the individual values of D-SVR between baseline and stimulation periods for the 22 patients are plotted in the Figure together with the corresponding changes in thermodilution SVR. 19 patients showed changes in the same direction for both Doppler and conventional SVR (16 increased, 2 decreased and 1 no change). In 3 patients, changes in D-SVR between the baseline and stimulation periods were in the opposite direction of the changes detected by conventional SVR.

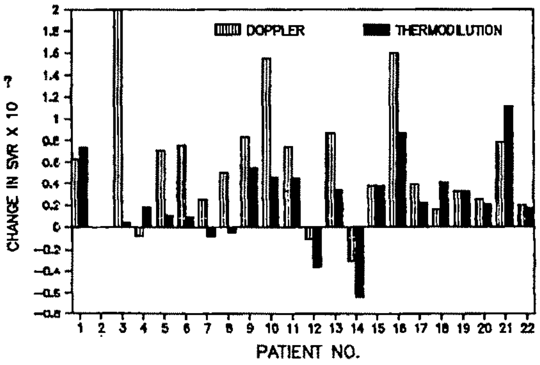
Discussion: Our findings demonstrate that values of SVR derived from Doppler ultrasound D-CO essentially follow SVR values determined by conventional means although the two are not always in agreement. No statistically significant differences were apparent between Doppler and conventional SVR during any of our measurement periods. On an individual basis, changes in D-SVR paralleled changes in conventional SVR in 19/22 patients. Individual changes in D-SVR had a tendency to exceed those in conventional SVR during the stimulation period. Interest in the Doppler technique to derive SVR is twofold: a) it is minimally invasive in the anesthetized or critically-ill intubated patient, and b) it can be used semi-continuously (with frequent input of MAP and CVP data). Since accurate, non-invasive determination of MAP by oscillometric devices (Dianamap®, Accutorr®, etc) exists, D-SVR could be determined automatically and continuously by entirely non-invasive means when willing to disregard the small error caused by ignoring the CVP. In the clinical setting, this presents new possibilities such as monitoring tissue perfusion changes in the critically-ill patient while in the clinical research area, it offers the advantage of a minimally invasive way to obtain SVR.

We conclude that esophageal Doppler measurements of CO can be used to determine SVR non-invasively. In light of the potential benefits, present deficiencies in the technique warrant further investigation.

TABLE
(# = significant, NS = not significant)

	D-SVR	(dyne-sec-cm^{-5})	SVR
BASELINE	1352±440	(NS)	1263±374
	(#)		(#)
STIMULATION	1959±955	(NS)	1516±538

FIGURE



Title: **EARLY EXTUBATION IN CHILDREN AFTER REPAIR OF ATRIAL SEPTAL DEFECT**

Authors: S. C. Hillier, MB, FFARCS, R. H. Taylor, MB, FFARCS, F. A. Burrows, MD, FRCPC

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Introduction: The postoperative management of children undergoing open cardiac surgery remains controversial. Studies suggest that early extubation, in selected cases, is not associated with increased morbidity or mortality.[1] Others have shown no impairment of lung compliance compared to non-cardiac controls.[2]

Prolonged intubation may lead to other tube related problems, such as subglottic stenosis, blockage and self-extubation.[3]

The present study was undertaken on a group of patients following repair of secundum atrial septal defect (ASDII) to determine if a difference existed between children extubated immediately postoperatively (Ex) compared to those remaining intubated (In).

Methods: After institutional approval, a chart review was performed using a single diagnosis of secundum ASD repair.

A total of 36 charts were examined. Age, weight, duration of cardiopulmonary bypass (CPB) and aortic cross clamp (XCL) at the time of surgery were recorded.

Anesthetic technique, including dose and type of opioid analgesic drug, was recorded from the anesthetic chart. Time to extubation and discharge from the Intensive Care Unit (ICU) were recorded as was the mean dose of morphine infusion used in the ICU.

pH and $PaCO_2$ were recorded from the first arterial blood gas analysis taken in the ICU. Complications and/or mortality were recorded if they occurred.

Unpaired Students t-test was used to compare the independent groups and chi-squared test for non-parametric data. Significance was accepted if $p < 0.05$.

Results: Nineteen children were extubated and 17 remained intubated and ventilated on arrival in the ICU. There were no patients requiring re-intubation and no deaths.

There were no differences in age or weight between the two groups. The group of In children had a longer duration of CPB, but the XCL times and sample numbers where XCL was used were not different (Table 1).

The number of patients in each group receiving fentanyl were similar. The In children had a higher dose of fentanyl (mcg/kg) when used as a sole opioid drug ($p < 0.05$) ($n = 12$). The dose of morphine (mg/kg) and sample numbers were similar for the two groups. Only one child in each group received meperidine.

The pH was lower in the Ex children and this was associated with a higher $PaCO_2$ ($p < 0.01$).

The group of In children had a higher rate of morphine infusion ($p < 0.05$) and a longer time to discharge from the ICU compared to those in the Ex group ($p < 0.01$).

Discussion: Patient characteristics were similar, apart from a prolonged CPB time in patients who remained intubated.

The differences in arterial blood gases, although significantly different, are within the clinical range and did not lead to re-intubation of any patient.

The association of prolonged intubation with higher doses of opioid does not imply a causual effect but probably reflects the bias of the individual anesthesiologist.

The surgery requires relatively short times on CPB which may help to attenuate postop cardio-respiratory problems.

This study suggests that early extubation after cardiac surgery, in selected cases, does not appear to cause any increase in mortality or morbidity.

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TABLE 1

	AGE (mos)	WEIGHT (kg)	CPB (mins)	XCL (mins)
Ex	69.5 ± 7.76	19.6 ± 1.86	23.3* ± 1.8	13.3 ± 2.22
In	72.9 ± 10.9	20.5 ± 3.08	31.7 ± 3.08	15.3 ± 2.05

Data are mean values ± SEM
*$p < 0.05$

TABLE 2

	DISCHARGE TIME (hrs)	FENTANYL (mcg/kg)
Ex	20.4* ± 0.84	5.9* ± 1.47
In	29.0 ± 2.72	35.1 ± 8.47

Data are mean values ± SEM
*$p < 0.01$

TITLE: CHANGES IN CEREBRAL BLOOD FLOW (CBF) AND CEREBRAL OXYGEN CONSUMPTION ($CMRO_2$) DURING N_2O IN UNANESTHETIZED UNRESTRAINED RATS

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Introduction: Increasing evidence suggests that N_2O will increase CBF and $CMRO_2$ in man and several animal species. The notable exception appears to be the rat.(1,2) Several investigations have reported that N_2O will not increase CBF, CMRgl and $CMRO_2$ in unrestrained rats. However the use of restraint in unanesthetized rats may be an issue.(3) In these experiments we measured CBF and $CMRO_2$ in unanesthetized unrestrained rats using radioactive microspheres.

Methods: Ten rats were anesthetized and surgically implanted with chronic femoral artery and vein, left ventricular and sagittal sinus catheters under isoflurane anesthesia. After a two hour recovery they were placed in a 9x12x30 cm enclosed chamber that was perfused with 70% N_2, 30% O_2 at a rate of 3 liters/min. After 15 minutes the first microsphere test was performed using Co-57 labelled microspheres. 70% N_2O was then substituted for N_2 and 15 minutes later a second microsphere test was performed using Sn-113 labelled microspheres. After an additional 45 minutes of 70% N_2O environment, a third microsphere test was performed using Sc-46 labelled microspheres. Chamber gases were analyzed continuously using a Datex anesthetic gas analyzer. Arterial blood gases and arterial-sagittal sinus O_2 content was measured at each microsphere test. This protocol was IACUC approved.

Results: Plasma epinephrine, measured before the first test, was 183±12 pg/ml, consistent with a non-stressed rat. Cortex and subcortex CBF were 126±10 and 97±7 ml.100g^{-1}.min^{-1} respectively and $CMRO_2$ was 10.0±0.5 ml O_2 100gm^{-1}.kg^{-1}.min^{-1} in unanesthetized N_2 treated rats. Cortex and subcortex CBF increased 100% and 40% respectively after 15 minutes of N_2O but $CMRO_2$ did not change significantly. CBF remained elevated after 60 minutes of N_2O. In a second group of rats (n-3), 2 tests made in an unanesthetized state showed no difference in CBF and $CMRO_2$ between the first and second test. A third test, made after paralyzing the rats and ventilating them with 70% N_2O, 30% O_2 showed a 150% increase in CBF and a 50% increase in $CMRO_2$.

Discussion: These results show that in unanesthetized unrestrained rats N_2O produces cerebrovasodilation but has little effect on $CMRO_2$. Paralyzation plus N_2O produces a further increase in both parameters. This questions the use of restraint in unanesthetized or N_2O ventilated rats or the use of N_2O for control measurements of CBF.

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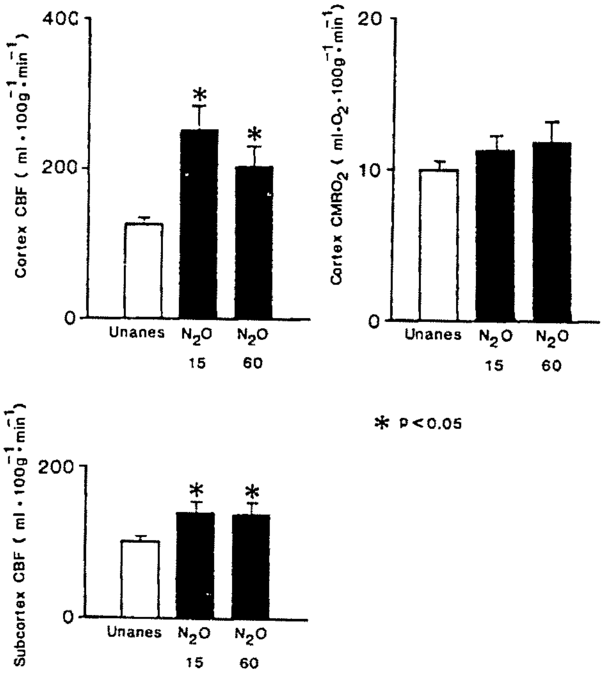

Figure 1. CBF and $CMRO_2$ during perfusion with 70% N_2 (Unanes) or 70% N_2O (N_2O), 30% O_2. Significance indicates difference from Unanes. Numbers under N_2O indicate time of perfusion.

Title: A COMPARISON OF MAXIMUM LENGTH SEQUENCE AND CONVENTIONAL CANINE BAERs DURING GRADED ISOFLURANE

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Introduction: A significant restriction of conventional intraoperative evoked potential recording techniques is the time required for data acquisition. Up to five minutes may be required to collect and replicate small amplitude signals in the noisy environment of the operating room. During this interval the surgical procedure may be interrupted, and neurologic structures in jeopardy may undergo further deterioration. Derivation of evoked responses by a new method using maximum length sequence (MLS) stimulation at rapid rates improves the efficiency of data collection by a factor of four to six times (1). In conventional averaging one electrophysiologic response to a stimulus must be complete prior to presentation of the subsequent stimulus. Using the MLS method, pseudorandom stimulus sequences are presented at rates faster than the latency of the evoked response, leading to convolution of the stimulus sequence with the evoked response. The nonoverlapped response is obtained from the observed response by cross-correlating the observed response with the input sequence. In this experiment the feasibility of MLS applications in the anesthetic setting was tested by comparing the fidelity of conventional and MLS brainstem auditory evoked responses (BAERs) recorded during graded doses of isoflurane. Because of its low amplitude, the BAER is associated with the smallest and most challenging signal to noise ratio of all the evoked potentials used as intraoperative monitors.

Methods: The experimental protocol was approved by the institutional research animal care committee. Anesthesia was induced in seven dogs with mask isoflurane. Endotracheal intubation and ventilation followed paralysis with metocurine. End-tidal CO2, temperature, and blood pressure were continuously monitored. Isoflurane was administered at 0.0%, 0.7%, 1.3% and 2.0% (Siemmens Servo Gas Monitor 120) in random order with 30 minutes at each level for equilibration before data collection.

Stimuli were 100 usec clicks at 100 dB SPL with 70 dB SPL masking delivered to the contralateral ear. Conventional and MLS stimulus trains were generated by an IBM PC, fit with an ASPI-DSP16 digital signal processing board. Conventional BAERs were collected at stimulus rates of 33.3 Hz and 100 Hz. MLS BAERs were collected at rates of 370 Hz and 1111 Hz. Evoked responses were recorded from vertex to ipsilateral mastoid by platinum subdermal needles. Responses were amplified 300,000 times and bandpass filtered 150-3000 Hz. All recordings were replicated. Peak latencies from onset, and positive peak to trough amplitudes were analyzed with a repeated measures ANOVA for factors of isoflurane dose, stimulus rate and dose-rate interaction. Pairwise T-tests were used to compare conventional and MLS components. A significance level of $P < 0.05$ was adopted for all comparisons.

Results: Both conventional and MLS responses closely resembled previously published canine BAERs (2)(figure). Wave I latency showed no effect of stimulus rate, isoflurane dose or dose-rate interaction with either conventional or MLS averaging techniques. A prominent and consistently recorded later peak, designated wave IV in accord with prior reports, demonstrated a significant prolongation of latency and reduction in amplitude with graded levels of isoflurane, but no effect of stimulus rate or dose-rate interaction in conventional recordings. Identical effects on wave IV latency and amplitude were detected in the MLS recordings. There was no significant difference in wave IV latency between conventional and MLS techniques at 0.0% isoflurane at slow stimulus rates. At 2.0% isoflurane wave IV latency was slightly but significantly prolonged in the MLS recordings in comparison to conventional averaging.

Discussion: The orderly and quantitative correspondence between conventional and MLS BAERs in absolute morphology, and in response to two experimental variables, isoflurane concentration and stimulus rate, suggests that recording fidelity is preserved with the MLS technique. The four to six fold reduction in time for data acquisition will permit earlier detection of neurologic injury, and less interference with the surgical procedure. Due to the immunity of BAER components to ambient noise when collected at very high rates of stimulation, MLS recording techniques may be ideally suited to unfavorable acoustic environments such as the operating room. However, encroachment on the absolute refractory period of neural generators at rates above 1200 Hz will impose a ceiling on the benefit to be gained at more rapid rates. Higher amplitude evoked potentials collected at longer latencies, and in response to other modalities of stimulation have more favorable signal to noise ratios than the BAER. Somatosensory and visual evoked potentials should therefore be especially amenable to MLS stimulation paradigms.

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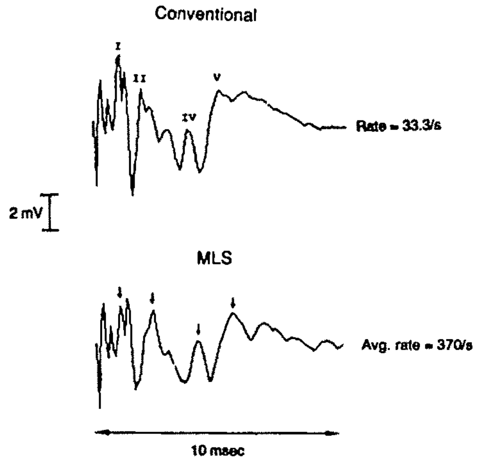
Figure Legend:



Representative conventional and MLS BAERs at 0.0% isoflurane.

Title: CYTOGENETIC ANALYSIS OF A MALE AND FEMALE WITH MALIGNANT HYPERTHERMIA ASSOCIATED WITH KING SYNDROME

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Introduction: Since first identified in 1973 (1), ten patients with King syndrome have been described. King syndrome consists of malignant hyperthermia (MH) in association with a slowly progressive myopathy and characteristic dysmorphic features including short stature, scoliosis, blepharoptosis, micrognathia, malar hypoplasia, downslanting palpebral fissures and low-set ears. Cryptorchidism, pectus deformities and familial elevation of creatinine phosphokinase (CPK) are variably present. Chromosomal deletions, translocations, and duplications that may give rise to dysmorphic features are detectable with a high degree of resolution by contemporary karyotyping techniques. To date cytogenetic analysis of King syndrome patients has been unavailable, with the diagnosis made retrospectively to the anesthesia-related death. The chromosomes of two King syndrome survivors of MH events were therefore examined.

Methods: With approval of the institutional human subjects committee, specimens were obtained from two previously reported patients, one a male(2) and the other a female (3).

Clinical Histories: The male patient was scheduled for cranial computed tomography with general anesthesia at age 7. Height and weight were below the third percentile. Dysmorphic features were malar hypoplasia, low-set ears, and scoliosis, with hypertonicity and hyperreflexia. The procedure was cancelled after he became rigid following administration of succinylcholine during thiopental and halothane induction. The highest recorded temperature was 37°C. CPK was 3744 U/L ten hours later. A muscle biopsy demonstrated increased contracture on exposure to halothane.

The female patient was to have a flap procedure for velopharyngeal leak at age 6. Downslanting palpebral fissures, ptosis, micrognathia, kyphoscoliosis and short stature were noted. Premedication with atropine and meperidine was followed by anesthetic induction with thiopental, pancuronium, nitrous oxide and halothane, but no succinylcholine. Within 15 minutes she developed tachycardia, hypercarbia, hyperthermia (38.6°C) and metabolic acidosis. Treatment with dantrolene, sodium bicarbonate and cooling led to a full recovery. The CPK peak was 4460 U/L at 19 hours. Elevated CPK levels were found in three generations of family members (maximum 560 U/L), in the absence of similar physical characteristics or a history of anesthetic complications.

Three additional King syndrome patients surviving acute MH triggers either died or were lost to medical attention before specimens could be collected.

Test Procedures: Mitotic cells in prometaphase and late prophase were derived from phytohemagglutinin stimulated lymphocytes by using standard 72-hour blood cultures and ethidium bromide treated cultures. The chromosomes were banded by the trypsin-Giemsa method. Twenty-five cells from each patient were analyzed under the microscope for chromosome number and structure, and a formal karyotype was prepared on two cells from each patient.

Results: All cells counted had a normal chromosome number of 46, with normal male and female karyotypes respectively. There was no evidence of chromosomal mosaicism or a structural abnormality.

Discussion: The association of the distinctive phenotype of King syndrome with MH suggests that the underlying cellular defect of at least one form of MH is dysmorphogenetic, perhaps as a consequence of expression of the myopathic process in utero. MH susceptibility inherited as an autosomal dominant trait in the absence of congenital anomalies may reflect a more restricted genetic error within the larger rearrangement responsible for King syndrome. The autosomal dominant elevation of CPK in three King syndrome pedigrees supports this hypothesis, however muscle biopsy and halothane contracture tests in family members at risk are required to further analyze the correlation. Evidence in the present investigation suggests that the chromosomal abnormality must be sought at the submicroscopic level using molecular genetic techniques including linkage analysis and gene cloning. In this fashion the true incidence of King syndrome, of MH associated with King syndrome, and the relationship of King syndrome to MH in other clinical settings will be determined.

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Title: THE CUMULATIVE DOSE-RESPONSE OF PIPECURONIUM BROMIDE IN CHILDREN

Authors: I. Hollinger, M.D., H. Nagashima, M.D., H.D. Nguyen, M.D., G.B. Bikhazi, M.D. and F.F. Foldes, M.D.

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Introduction: Pipecuronium bromide, a nondepolarizing neuromuscular (NM) blocking agent with similar chemical and pharmacological properties to pancuronium, has been investigated clinically in adults (1,2). It has been reported that the NM potencies of vecuronium in infants and children are not different from those in adults (3). Goudsouzian and his associates (4) found, however, that in children the dose-response regression line of vecuronium was shifted to the right from that of adolescents, indicating that the dose requirement of vecuronium in children was more than in adolescents. The present study was designed to determine whether there are any age related differences in the NM effects of pipecuronium.

Methods: This study, approved by the Institutional Review Board was carried out on 21 ASA classification 1, 2 and 3 children of 1 to 14 years of age whose guardians signed informed consents. Patients were premedicated with 1.0-1.5 mg/kg diphenhydramine, 1.0-1.5 mg/kg meperidine and 0.01 mg/kg atropine intramuscularly an hour prior to surgery. All drugs administered during anesthesia were given intravenously. Anesthesia was induced with 0.05 mg/kg droperidol, fractional doses of fentanyl and N_2O-O_2. To facilitate early application of electrical stimulation of ulnar nerve, 2.0 mg/kg of thiopental was added to the induction agents. Anesthesia was maintained with 4 l/min N_2O-2 l/min O_2 and fentanyl. After induction of anesthesia, electrodes were placed over the ulnar nerve at the wrist and stimulated with train-of-four (TOF) supramaximal square wave pulses of 0.1 msec duration administered at 2 Hz every 10 sec. The elicited electromyogram (EMG) of the adductor pollicis muscle was continuously recorded. After obtaining a control tracing 10 µg/kg pipecuronium followed by 5 to 10 µg/kg increments were injected i.v. until greater than 85% block developed. Each dose was injected when the maximal effect of the previous dose had developed. The "cumulative" log dose-response (T1 of TOF) regression lines of pipecuronium were determined for each subject and ED50 and ED90 values were calculated. To maintain surgical relaxation 15 µg/kg increments of pipecuronium were administered whenever T1 returned to 25% of control. When T4/T1 ratio was < 0.75 at end of anesthesia the residual NM block was antagonized with a mixture of 40 µg/kg neostigmine and 15 µg/kg atropine. The results obtained were compared (Student's *t* test) with those obtained in adults (2).

Results: As indicated in the table, pipecuronium is less potent in children than in adults. In contrast to adults the clinical duration of successive maintenance doses of pipecuronium was unchanged in children. Residual NM block could be antagonized equally well in adults and children.

Discussion: The findings presented indicate that in children pipecuronium is less potent than in adults. Our findings are in contrast to those reported by Fisher (3) indicating that the ED50 of vecuronium does not change with age. They stated that this was due to the fact that age-related changes in the steady state volume of distribution and plasma concentration of the relaxant, that caused 50% depression of the twitch, counterbalance each other and result in no change in ED50 values. In contrast to the considerable cumulative effect of pipecuronium observed in adults (2), there was no cumulative effect in children.

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Neuromuscular Parameters in Children and Adults

Parameters	Children	Adults	p <
ED50 (µg/kg)	28.3±2.0(21)*	20.3±1.1(28)	0.001
ED90 (µg/kg)	55.8±4.6	35.1±1.7	0.001
Clinic Durat(min)			
Maintenance Doses			
1st Dose	29.8±3.0(12)	31.3±2.9(21)	n.s.
All Doses	26.8±1.5	47.1±2.0(38)	0.001
Recovery Rate(min)	24.5±10.7(3)	44.5±8.2(3)	n.s.

*Mean±SEM of number of observations in parenthesis.

Title: EVALUATION OF CONTINUOUS FEMORAL NERVE ANALGESIA AFTER PRIMARY TOTAL KNEE ARTHROPLASTY

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Introduction:

After total knee arthroplasty (TKA), postoperative pain management is crucial, since pain limits the progression of knee extension and flexion. By providing adequate analgesia, more rapid progression of joint motion may be obtained, so that the patient has greater final mobility of the knee and may be discharged from the hospital earlier. Patient-controlled analgesia (PCA) with intravenous opioids has been used routinely in our patients for pain management. However, PCA does not prevent quadriceps spasm or completely relieve pain during postoperative continuous passive motion (CPM). Femoral nerve blocks have been used for pain relief,[1-3] but no controlled study has evaluated the efficacy of continuous femoral nerve analgesia (FNA) after TKA.

Methods:

This study was approved by the Human Investigations Committee of Emory University, and written informed consent was obtained. Patients were randomized to two groups. Group I did not receive FNA. Patients in Group II had catheters placed into the femoral nerve sheath. A Contiplex^R (Burron) needle/catheter was advanced one fingerbreadth lateral to the femoral artery in the inguinal crease until quadriceps contraction was obtained with less than 0.5 mAmps using a peripheral nerve stimulator (Stimuplex-s^R - Burron). After withdrawal of the needle, a 20-gauge polyamide catheter was inserted 5-10 cm through the 18-gauge teflon catheter. The 20-gauge catheter was then secured with adhesive strips and a transparent dressing. In the recovery room, 10 ml of bupivacaine 0.25% with epinephrine 1:200,000 was injected through the femoral catheter. The patient was then started on a continuous infusion of bupivacaine 0.25% at 7 ml/hr. For inadequate analgesia, patients were given a 10 ml bolus of bupivacaine 0.25% and the infusion rate was increased by 2-4 ml/hr. A PCA device containing morphine was attached to an intravenous cannula in both groups.

In the recovery room, the patient's leg was placed in a CPM machine, and daily increases of both flexion and extension of the knee were made by the physical therapist as tolerated by the patient's level of pain. The angle of maximum knee extension and flexion was measured daily.

Pain was assessed using a verbal rating scale (0 = no pain, 10 = unbearable pain) and the total dose of morphine used by the patient was recorded for each shift postoperatively.

Results:

Twenty-two patients completed the study. The results are shown in Table 1. The time to 80° flexion (Flex 80) was significantly shorter in Group II. Pain ratings on the first postoperative day (Pain 1) were lower. There was no difference in total morphine (Tot MS) used in the first 24 hours, or the pain ratings on the second postoperative day.

Discussion:

Pain after TKA is associated with protective spasm of the quadriceps muscle. The femoral nerve innervates the quadriceps and the anterior and medial knee. However, the lateral femoral cutaneous, tibial, common peroneal, and obturator nerves also innervate the joint, and patients continue to have pain which requires the use of potent opioids despite FNA. Patients with FNA had less pain, while reaching 80° flexion more rapidly than those patients with only PCA. This ability to rapidly progress rehabilitation of the knee without increasing pain or opioid requirements is felt to be a significant advantage of FNA following TKA.

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Table 1

	I n=12	II n=10
Flex 80° (d)	7.1	5.2*
Pain 1	5.4	3.2*
Tot MS (mg)	42.0	34.0
Pain 2	3.6	3.1

* $p < 0.05$

TITLE: A RANDOMIZED COMPARISON OF INHALATION VERSUS NARCOTIC ANESTHESIA FOR MITRAL VALVE REPLACEMENT

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Patients with valvular heart disease frequently have compromised ventricular function due to chronic volume and/or pressure overload and secondary pulmonary hypertension. Narcotic anesthesia has become widely accepted for mitral valve replacement surgery (MVR), with the advantages of lack of myocardial depression, slower heart rate, and stable arterial pressure. A property of a predominantly isoflurane anesthetic technique during MVR would be a vasodilating effect on both the systemic and pulmonary vasculature, which may be beneficial to both left (LV) and right ventricle (RV) function in MVR patients.

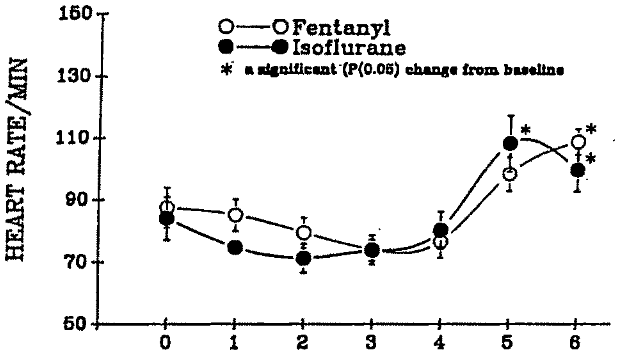
In a controlled trial, we compared these two techniques for induction and maintenance of anesthesia until 10 min after protamine administration during MVR surgery.

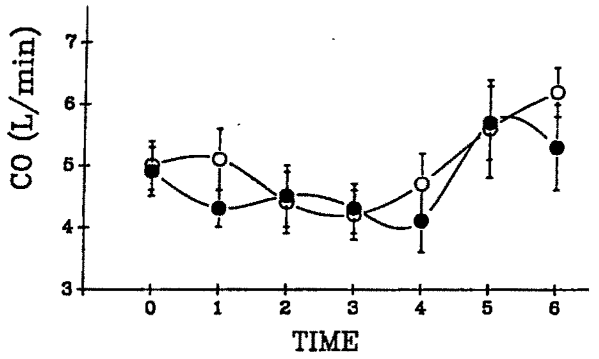
Methods. Nineteen consenting patients scheduled for MVR with mean PAP greater than 35 mmHg were randomized into two groups to receive either high-dose fentanyl anesthesia (induction with fentanyl 50 mcg/kg and vecuronium or pavulon 0.1 mg/kg, and fentanyl maintenance with 0.5 mcg/kg/min) or an isoflurane anesthetic technique, with thiopental 1-3 mg/kg, vecuronium or pavulon 0.1 mg/kg, and isoflurane 1-2% for induction and isoflurane 1-2% for maintenance.

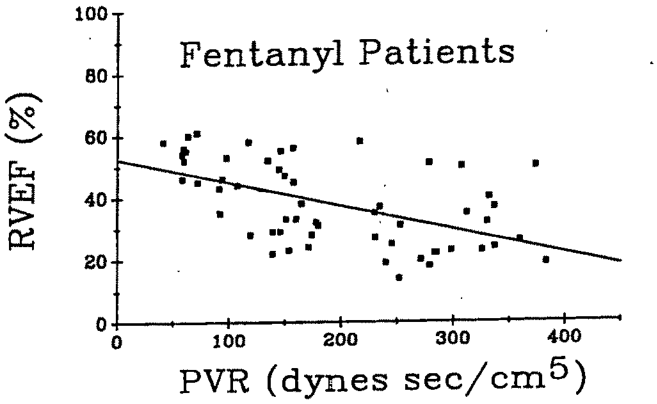
Evaluation of right ventricular performance was enhanced by a RVEF Swan-Ganz pulmonary artery catheter (American Edwards model 93A 431 H-7), which allows calculation of right ventricular ejection fraction, stroke volume, end systolic and end diastolic pressures. Full hemodynamic profiles were taken in triplicate at baseline, 5 min after induction, 5 min after intubation, prior to skin incision, 5 min after sternotomy, after 10 min of cardiopulmonary bypass, and 10 min after protamine was given (events 0,1,2,3,4,5,6 respectively).

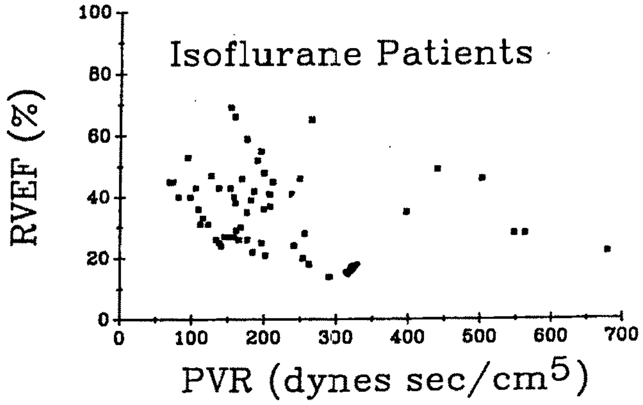
Results. Premedications and demographic data were similar in both groups of study patients. HR (Fig 1), CO (Fig 2), CVP, MPAP, PVR and SVR were similar in both groups. MAP and SAP were significantly lower than baseline from induction until after protamine administration in the isoflurane group, but without evidence of decreased LV function. CO remained at baseline levels in both study groups. RVEF was well maintained in the fentanyl subjects, but declined from baseline in the isoflurane group (42% to 29%) after sternotomy without associated changes in CVP or PVR. Cardiac output was negatively correlated with PVR in both study groups. RVEF and SV were negatively correlated ($r=-0.5$, $p<0.01$; $r=-0.6$, $p<0.01$) with PVR in the fentanyl patients (Fig 3) but uncorrelated in the isoflurane patients (Fig 4). CVP was negatively correlated ($r=-0.5$, $p<0.01$) with RVEF in the fentanyl patients but uncorrelated in the isoflurane patients.

Conclusion. The findings that MAP & SAP were decreased from baseline in the isoflurane group were anticipated and represent isoflurane-induced vasodilation. However, because none of the patients were beta-blocked, the finding of similar heart rates between groups is surprising. In the isoflurane group, the fact that the decline in RVEF was not correlated to either CVP or PVR (ie, not related to changes in preload or afterload) may represent isoflurane-induced RV decompensation. Although there was no evidence of LV dysfunction, the fact that LV function did not improve with decreased afterload in the isoflurane group may represent a decrease in LV performance. Standard PA catheter readings and derivations were not sensitive to changes in RV function, emphasizing the need for judicious clinical assessment of RV function in cases where such function may be jeopardized.









Title: ARE INTRAOPERATIVE COMPLICATION RATES INFLUENCED BY ASA PHYSICAL STATUS, AGE, AND EMERGENCY VS. ELECTIVE STATUS?

Authors: J.C. Hudson, M.D., K.S. Dawson, M.S.*, F.R. Kane, Ph.D., B.L. Tyler, R.N., R.L. Keenan, M.D.
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Introduction: Clinical data were collected since 1984 to search for factors that influence anesthetic outcome. Our hypothesis was that intraoperative complication rates (ICR) increased with increasing ASA physical status (ASA). We then evaluated the influence and possible interaction of age and emergency status (Emer), i.e., nonelective cases as compared to elective (Elec) upon these rates within each ASA.

Methods: Data collected over 5 years from 7/84 until 6/89 composed of 63,939 cases from a 1000-bed university hospital were analyzed. Complications were categorized: cardiac (C), respiratory (R), metabolic (M), and other (O) [renal, blood/drug reactions, etc.]. A case was considered as having a complication if the primary anesthetist identified one or more problems within the category. Every record was reviewed for accuracy and entered into the database (Digital VAX-750). Logistic regression (LR) was used for analysis. This builds a model describing the ICR as a function of the suggested factors (ASA, age, Emer/Elec). Age categories were <1, 1-9, 10-24, 25-39, 40-54, 55-69 and >69 years. Because ASA was a significant effect ($p<0.0001$) separate LR was applied to each of the categories ASA (1-4) to determine the influence of age and Emer. The Bonferroni correction was used in order to account for the fact that there are 3 tests within each of 4 groups. Therefore, the α level is decreased to $(0.05/3\times4)$; a p value < 0.0042 was considered significant.

Results: In C, R, O: 1) an increase in ASA is associated with a significant increase in ICR ($p<0.0001$) (Fig. 1); 2) within each ASA (1-4), an increase in age is associated with a significant increase in ICR ($p<0.002$) independent of ASA (Fig. 2); 3) Emer is associated with a significant increase in ICR in ASA 3 and 4 ($p<0.002$) (Table 1).

COMPLICATIONS
ELECTIVE CASES ONLY

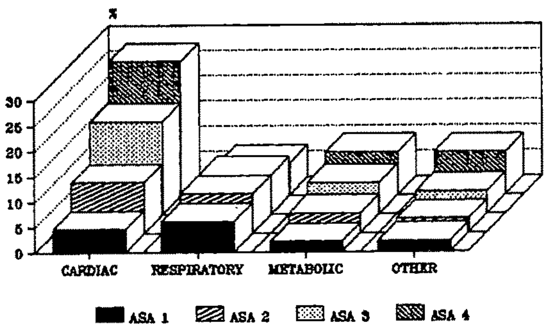

Fig. 1

COMPLICATIONS
CARDIAC

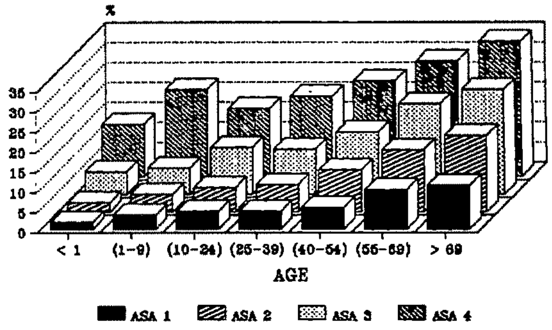

Fig. 2

Table 1

Complication Rates
% Cases with 1 or more in category

ASA	Cardiac		Resp.		Meta.		Other	
	Elec	Emer	Elec	Emer	Elec	Emer	Elec	Emer
1	4.57	3.01	6.08	4.13	2.01	2.01	2.16	1.42
2	10.11	7.48	7.77	7.05	3.86	4.47	2.75	2.88
3	18.33	18.35	7.77	7.07	6.17	9.02	4.42	6.07
4	26.42	36.40	6.28	10.59	8.41	18.89	8.36	15.50
All	13.20	19.85	7.34	8.20	4.68	10.46	3.68	8.06
Overall Category Rate								
	14.11		7.46		5.47		4.28	

In R: ICR are not significantly affected by Emer, although a trend is evident. The only significance between ASA and ICR is that ASA 1 Elec is lower than other ASA groups ($p<0.001$) (data not shown). Similarly, age has no effect in R other than in ASA 4 where it is associated with a significantly lower ICR ($p<0.0001$).

Discussion: These data support the hypothesis that increasing ASA, age, and Emer status influence ICR. The effect of ASA is consistent with increasing systemic disease. Advancing age alone is associated with increasing ICR within each ASA category. Emer has no additional influence in ASA 1 and 2 but is associated with increase in ICR in ASA 3 and 4 when systemic disease is moderate to severe.

In R the ICR are relatively flat. Several of the problems in this category reflect variation in anatomy of the airway and occur randomly. The decrease in ICR in ASA 4 may reflect decreasing airway irritability with age and/or arrival in the OR with endotracheal tubes in place.

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Title: THE MULTICENTER PULMONARY ARTERY CATHETER STUDY: THE IMPACT OF EDUCATION AND EXPERIENCE

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Introduction: Recent editorials and research reports question the risk versus benefit ratio of the pulmonary artery catheter (PAC) (1-3). The PAC is a diagnostic tool that can only be of benefit if the data it yields are properly interpreted and used in determining therapy. Despite widespread use of the PAC by a variety of adult-care providers with differing levels of training, to our knowledge, neither the adequacy nor consistency of users' knowledge about the PAC has been studied. We undertook a multicenter study to determine whether those routinely using the PAC have sufficient command of the principles underlying its placement, data management and interpretation to safely and effectively utilize it.

Methods: Sixteen intensivists from 14 institutions in the US and Canada employed a three-phase iterative process to compile a 31-question, criterion-referenced multiple-choice examination. The examination included questions on PAC insertion and complications (6 questions), cardiac physiology (3), interpretation of data (14), and use of data in patient management (8). The questionnaire was pilot-tested in 2 university hospitals. Following minor changes in the wording of responses to 4 questions, the exam has been administered virtually unchanged in an additional 12 sites.

Results: Examinations administered to the 121 physicians participating in the pilot test were analyzed. The mean test score was 21 (68%) with a range of 9-31 (29-100%). While the mean percent correct for each of four subtests was approximately 67%, respondents had greater difficulty with questions regarding interpretation of PAC data (55% with <70% correct) and patient management (45% with <70% correct) than with those related to PAC insertion/complications (31% with <70% correct) or cardiac physiology (22% with <70% correct).

Mean scores varied independently by both training (p=.0001) and frequency of use of PAC data in patient management (p=.0001) (See Figure 1). Although anesthesiologists had the highest overall mean score (See Table 1), differences among the 3 major specialties represented were not statistically significant (p=.08). Observed differences reflected variations in the distribution by training of respondents from each specialty.

Respondents' perceptions of their own knowledge were reflected in test scores. Those who considered their knowledge about the PAC to be inadequate for their level of responsibility had a mean score of 52%, while those who felt their knowledge was adequate or more than adequate had mean scores of 69-71%.

Discussion: The substantial variations observed in test results indicate that any attempt to determine the PAC risk-benefit ratio on the basis of studies published to date will be severely hampered by their lack of control for differences in training and experience among providers using PAC data. In addition, the similarity between centers in the range of test results strongly suggests a need to evaluate the process by which users are trained in interpretation and utilization of PAC data for patient management.

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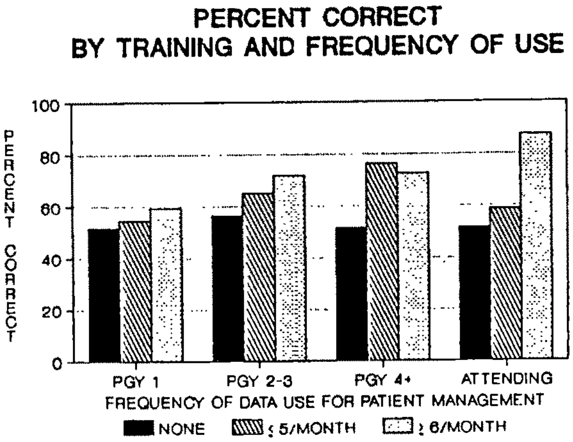
TABLE 1

MEAN SCORES AND PERCENT CORRECT BY SPECIALTY

	Number of Respondents	Mean Score	Percent Correct
Anesthesiology	40	21.5	69.4
Internal Med.	68	21.3	68.7
Surgery	10	18.5	59.7

FIGURE 1



Title: INCIDENCE OF MYOCARDIAL INFARCTION AND MORTALITY AFTER CORONARY ARTERY SURGERY ARE HIGHER WITH ISOFLURANE THAN WITH ENFLURANE ANESTHESIA

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Introduction: Laboratory as well as clinical studies (1,2) have suggested that isoflurane may produce myocardial ischemia by coronary steal in patients with coronary artery disease. On the contrary, others found no such deleterious effects of isoflurane (3), or reported even its beneficial effects in pacing-induced ischemia (4). Thus, question remains as to whether there is a relationship between the choice of anesthetic agent and postoperative outcome, particularly whether the use of isoflurane is justified in patients undergoing coronary artery bypass grafting (CABG). In view of this, we examined the influence of isoflurane and enflurane on the incidence of postoperative myocardial infarction (MI) and/or death in a large patient population.

Methods: With institutional ethical committee approval and informed consent, the use of primary anesthetic agent, isoflurane or enflurane, was alternated on a weekly basis in all operating rooms. 1178 patients undergoing elective CABG without additional operations were prospectively studied from February 27, 1987 to April 29, 1988.
Anesthesia was induced with methohexital following fentanyl 0.2-0.4mg. Tracheal intubation was facilitated by succinylcholine. Before sternotomy, additional doses of fentanyl 0.1-0.3mg (total 0.5mg including the induction dose) were administered. Anesthesia was maintained with the volatile agent assigned and nitrous oxide (50%) in oxygen. Vecuronium was used for muscle relaxation.
The inspired concentration of volatile agent was adjusted depending on the level of blood pressure at the discretion of the anesthesiologist. Additionally, nitroglycerin and/or nifedipine were administered intravenously, if necessary.
In 1003 cases, distal anastomoses of vein grafts were performed without cardioplegia by clamping the aorta intermittently. In 175 cases, distal anastomoses were performed after the infusion of cold cardioplegic solution into the aorta. During cardiopulmonary bypass (CPB), hypertension and hypotension were treated primarily by changing the concentration of volatile agent.
Blood was taken for CK and CK-MB analysis on the morning of the first postoperative day in all patients. A 12-lead ECG was obtained routinely on arrival in the ICU, on the morning of the first postoperative day and one day before discharge (usually 3rd to 9th postoperative day). MI was considered present when new Q waves appeared and when CK-MB was in excess of 40 U/l. Mortality denotes in-hospital mortality.
Significance of differences in mean values were tested by Student's t-test for unpaired data. Frequency data were tested by Chi-square analysis. $P<0.05$ was considered significant.

Results: As their primary anesthetic agent, 570 patients received isoflurane and 608 enflurane. Both groups were similar in the risk factors (Montreal Heart Institute Risk Classification Index) and in other patient characteristics. There was also no difference between the groups in the assignment of 7 surgeons and in surgical characteristics.
Of 570 patients who received isoflurane, 12 (2.1%) died (Table). 11 deaths occurred primarily due to pump failure or dysrhythmias: In six patients, hemodynamic aberrations commenced in the operating room, in three, immediately after arrival in the ICU and in two, 6 and 9 hours after arrival in the ICU. Seven of them had ECG evidence of MI and were included in the group considered to have MI.
The 12th patient died from multisystem failure.
Of 608 patients who received enflurane, two (0.3%) died. In these patients, hemodynamic aberrations commenced in the operating room and were considered to be attributable to MI.
The difference in mortality between the isoflurane and enflurane groups was significant ($p<0.01$).
23 patients (4.0%) who received isoflurane and 11 patients (1.8%) who received enflurane suffered MI. The difference was also significant ($p<0.05$).

Discussion: Our results contrast the recent report of Slogoff and Keats (5) who found no difference in mortality and incidence of MI between the primary anesthetic agents isoflurane and enflurane.
In both studies, volatile agent was continued until start of CPB. During CPB, volatile agent was not always used in their study but in ours it was used in all patients. If CPB was the period when deleterious effects of isoflurane became manifest, this difference in the management during CPB may have resulted in different findings.
In summary, our data clearly demonstrated a strong relationship between the choice of anesthetic agents and outcome when they are used in the manner usual in clinical practice. Accordingly, the use of isoflurane is not justified in patients undergoing CABG.

Table: Incidence of postoperative MI and mortality

	Isoflurane (n=570)	Enflurane (n=608)	
MI	23 (4.0%)	11 (1.8%)	$p<0.05$
Deaths	12 (2.1%)	2 (0.3%)	$p<0.01$

References:

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Title: Anesthetic Implications in Myocardial Revascularization Without Cardiopulmonary Bypass
Authors: W. B. Isaacs,MD, J. Matsumura,MD, C.A. Schmidt,MD, S.Kwik,MD
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Introduction

Since the late 70's Coronary Bypass surgery (CABG) has been primarily performed on the arrested heart. There have been several studies reported in the surgical literature that have suggested safety and efficacy in grafting of Left Anterior (LAD) descending and Right Coronary arteries (RCA), while not using extracorporeal circulation (CPB) to provide a "quiet" surgical field. The problems encountered with providing an anesthetic for this surgical technique have not been described. This technique of surgery has been recently introduced into our institution. We will describe the anesthetic implications and results of such surgery with regard to hospitalization, decreased blood utilization, and safety of the procedure for the patient.

Methods

With institutional approval and consent eleven patients underwent CABG surgery without CPB between 2/7/89 and 7/13/89 by the same Thoracic surgeon. These patients were compared with patients undergoing CABG with CPB, as controls, during the same period of time with the same surgeon. The non-CPB patients were limited to vessel lesions in LAD, RCA, and Diagonal systems. The patients were uniformily monitored with pulmonary artery catheters and standard anesthetic monitors. The anesthetic technique that was used was primarily high dose fentanyl(50-100ug/kg), oxygen, relaxant. Heparin 100u/kg was administered prior to anastamosis. The patients' charts were reviewed and compared analyzing the need for vasopressors, arrythmias, age, days of post-op hospitalization, blood unit exposures, number of vessels bipassed, and on the non CPB patients myocardial enzymes were evaluated as well. The patients were also selected for being elective CABG surgeries.

Results

A total of 22 patients were reviewed for this study. The data on the differences of the non CPB patients and patients that used CPB are in the table below. The data on blood transfused , and hospital stay are significant. No patient had any positive myocardial enzymesincluded within the study have had positive myocardial enzymes. Patients have been done that were emergency CABG without CPB and those patients did have positive enzymes.

	No CPB	CPB	P Value
# patients	11	11	
Age	65.6±10	65.1±9.9	NS
#Grafts	2.2± .9	3.0±1.1	NS
Banked RBC's	.45±1.0	2.1± 1.7	<.02
Platelets	0	6.7± 5.7	NV
FFP	0	1.4± 2.0	NV
Post-op Stay	4.6±0.93	7.8 ± 2.6	<.001

P values determined with students' t test. The anesthesia difficulties with the non CPB surgeries were limited to tachy-arrhythmias, PVCs', and hypotension caused by manipulation of the heart. Esmolol was used to control the arrhythmias, and the frequency of premature ventricular contractions seems to be decreased as well with this therapy. Surgeons preferred the effect of the controlling the heart rate from 60-80 because of the stability of the surgical field that was maintained. The cardiac output as measured by thermodilution increased after each vessel was anastamosed.

Discussion

Advantages of performing CABG without CPB include more rapid recovery resulting in shorter hospitalization and reduced costs. There is also decreased blood requirement due to reduced blood trauma and less disruption of the coagulation system. Even with a small study group, we were able to demonstrate shorter post-op hospitalization and decreased banked blood requirement with similar mortality, safety and efficacy. We have also not encountered any anesthetic difficulties that have been insurmountable. The use of esmolol has helped in the prevention of tachy arrhythmias, decreasing myocardial oxygen demand and provides a surgical field that is technically easier to operate upon. Further studies will compare graft patency, reversal of exercise induced ischemic changes,and more definitive evidence for perioperative myocardial ischemia and match the patients for ventricular function.

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Title: SIMPLE COMPUTERIZED MEASUREMENT OF PULMONARY CO_2 OUTPUT PER BREATH IN DOGS

Authors: SA Isserles MD, BA Harrison MBBS, AV Montano BSc, & PH Breen MD

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Introduction. During anesthesia, measurement of pulmonary CO_2 output per breath (VCO_2/br) could aid the early diagnosis of changes in metabolism (eg. malignant hyperthermia) and non-invasively measure changes in cardiac output (1). VCO_2/br is given by integrating $\dot{V}(t) \cdot FCO_2(t) \cdot dt$ for each breath ($\dot{V}$, pneumotachometer expired flow; FCO_2, side-steam infrared CO2 fraction; dt, time interval) (2). We describe a simple computerized measurement of VCO_2/br and its validation in dogs.

Methods: This study was approved by the Animal Research Committee of the University of Chicago. Due to suctioning through the capnometer sampling tube, the measured FCO_2 (Fig.1, FCO_2 "A") is time delayed (TD) behind $\dot{V}$. We measured TD in a bench set-up (bench TD) by plunging the capnometer sampling tube tip (Engstrom Eliza or Ohmeda 5200) into a beaker of 5% CO2 covered with tinfoil. At contact with the tinfoil, an electrical circuit generated a voltage to signal zero time. TD is the time to reach 5% of peak CO_2.

FCO_2 and $\dot{V}$ signals are digitized at 100 Hz and stored in a microcomputer. We have developed software algorithms that correct FCO_2 for TD (Fig.1, FCO_2-"B") and for instrument response lag (2) before VCO_2/br is calculated. In chloralose-urethane anesthetized and ventilated dogs (20-25 kg), we measured VCO_2/br during various ventilation patterns (positive end-expired pressure (PEEP) 0-10 cmH_2O; respiratory rate (RR) 4-21 min^{-1}; tidal volume (V_T) 10-20 ml/kg; anatomical dead space (V_D) 20-200 ml).

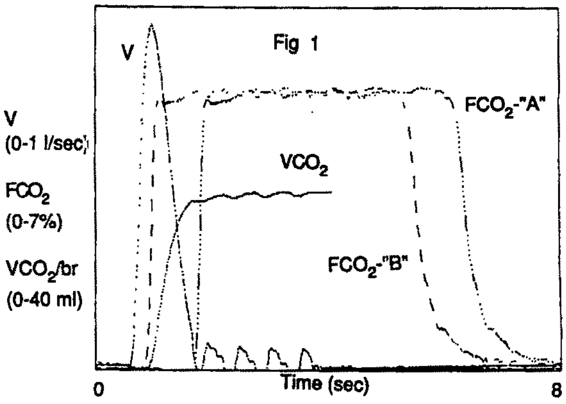

Fig 1

Results: Results are expressed as mixed expired fraction of CO_2 in each breath ($FmeCO_2$/br), where $FmeCO_2/br = VCO_2/br \div$ tidal volume. Fig.2a displays the correlation (r=0.79) of $FmeCO_2$/br (calculated using the bench TD) compared to $FmeCO_2$ measured in simultaneous mixed expired gas collections ($FmeCO_2$[coll]), over the range of ventilation patterns.

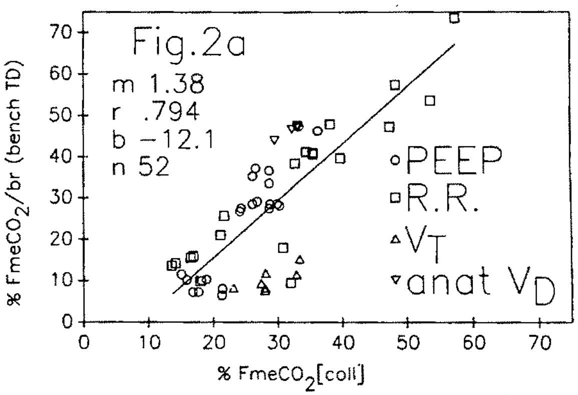

Fig.2a

We reasoned that the effective TD could differ from the bench TD due to different sampling configurations and circuit dimensions of side-stream capnometers. To test this hypothesis, using baseline ventilation data, another computer routine iteratively adjusted the bench TD until $FmeCO_2$/br equalled $FmeCO_2$[coll]. When this effective TD was used to calculate $FmeCO_2$/br over a wide range of experimental changes in ventilation (Fig.2b), we attained significantly better ($p<.05$) correlation (r=0.95) with $FmeCO_2$[coll].

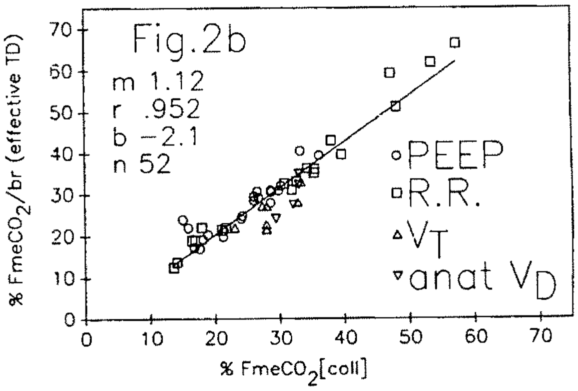

Fig.2b

Discussion: Capnometer time delay (TD) data from manufacturers or measured in bench circuits are unreliable for VCO_2/br. Our in-vivo determination of effective TD in any experimental or clinical circuit is swift, can be shown to be independent of FCO_2 and $\dot{V}$ calibrations, and generates accurate VCO_2/br determinations.

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Supported by: Foundation for Anesthesia Education & Research.

Title: LOW DOSE CLONIDINE ENHANCES PREGNANCY INDUCED ANALGESIA TO VISCERAL BUT NOT SOMATIC STIMULI IN RATS

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Introduction: There is a general clinical impression that a parturient has a lowered requirement for anesthetics and analgesics. Previous work has demonstrated the adequacy of colorectal distension as a visceral stimulus for use in pregnant rats and also confirmed the existence, in rats, of preganancy-induced, naloxone-reversible analgesia, an analgesia that influenced both somatic and visceral stimuli.[1] Several studies have reported an enhancement of opiate analgesia following the administration of clonidine by several different routes. This is one of a series of ongoing experiments designed to examine the pharmacology of pregnancy-induced analgesia in the rat. We hypothesized that since pregnancy-induced analgesia is naloxone reversible and clonidine has been shown to enhance opiate analgesia that low doses of clonidine would increase pregnancy-induced analgesia.

Methods: This protocol was approved by the Yale University Animal Care and Use Committee. Experiments were performed on unanesthetized female Spague-Dawley rats, weighing 250-300g at the start of the experiments. Two tests (colorectal distension, tail-flick) were used to assess each animal's response to painful visceral and somatic stimuli. The colorectal distension apparatus and methods were modified from Ness and Gebhart.[2] Colorectal distension involved inflation of a balloon that had been inserted intra-anally into the colon and rectum under light halothane anesthesia. Animals were awake during testing. Air pressure within the intracolonic balloon was steadily increased at a rate of 2mm Hg/sec until contraction of abdominal musculature was detected. The pressure at which abdominal constrictions were triggered by balloon distension was defined as the threshold response of colorectal distension, Control values were similar to those reported to be aversive in awake rats.[2] Standardized tail-flick testing was employed by monitoring latency to withdrawal from a heat source focused on a distal segment of the tail. After determining baseline values, animals (n=27) were mated and retested on Day 7 and 21 of gestation and 7 days after parturition. Immediately after testing on those days, animals received 0.1 mg/kg clonidine subcutaneously (doses based upon weight on Day 7) and were retested. In addition, 20ug/kg of naloxone (dose based on weight on Day 21) was administered intravenously in 9 pregnant rats on Day 21 of gestation 20 min after the administration of clonidine and animals were retested 15 min later. Each test was repeated six times at each time point with a 30 second intertrial interval. The mean of the last three tests at each test time point was used for analysis and is reproted here. Student's t test was used to evaluate statistical significance.

Results: As shown in Figure 1, pregnant animals demonstrated a statistically significant increase in pain threshold for colorectal distension and tail-flick on Day 21 of gestation. Colorectal distension thresholds following 0.1 mg/kg clonidine on Day 7 of gestation and postpartum Day 7 were not significantly different from pre-clonidine values. In contrast, on Day 21 of gestation, there was a significant increase in colorectal distension thresholds compared to pre-clonidine values. This increase in pregnancy induced analgesia was apparent at 10 min, with a peak effect at 30 min, and persisted for about 1 hour after clonidine administration. The potentiating effect of 0.1 mg/kg clonidine on Day 21 of gestation was reversed to pre-pregnant baseline values by 20 ug/kg naloxone administered intravenously. Clonidine produced no significant change in tail-flick latencies.

Discussion: As previously demonstrated,[1] pregnancy-induced analgesia to visceral and somatic noxious stimulation is evident late in pregnancy in rats. Systemic clonidine, at a dose lower than that required to produce significant antinociception, enhanced the pregnancy-induced analgesia to noxious visceral stimulation late in pregnancy. The potentiating effect of clonidine was completely antagonized by naloxone. These findings strongly suggest that the synergistic antinociceptive effect of clonidine is produced by an interaction with an endogenous opiate system that is only active near the time of parturition (no similar effect was seen on Day 7 of gestation or post-partum Day 7). The absence of a clonidine effect on tail-flick latencies suggests that there is a selective effect on visceral stimuli. Since a major part of pain sensation in labor is associated with visceral nociception from the uterus, cervical and peritoneal fibers, the synergistic interaction that we observed in this study may prove to be clinically useful in the design of labor pain control strategies. It may also suggest ways to enhance endogenous pain control mechanisms. Selectivity for visceral stimuli has been associated with kappa opiate receptors and kappa opiate receptors have been associated with pregnancy-induced analgesia in rats. The selective effect on visceral stimuli in this study may be due to an alpha-adrenergic--kappa opiate interaction.

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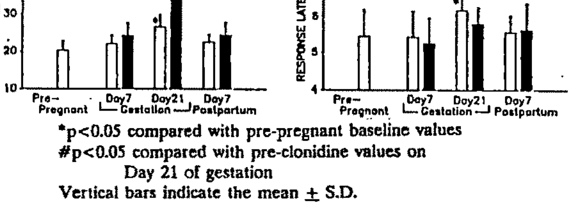

*$p<0.05$ compared with pre-pregnant baseline values
#$p<0.05$ compared with pre-clonidine values on Day 21 of gestation
Vertical bars indicate the mean ± S.D.

Title: Is Propofol a Muscle Relaxant?

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Introduction:

A number of publications report propofol's muscle relaxant properties such that intubation may be performed without paralyzing patients.[1] We evaluated propofol after induction and during mainterance with N_2O-O_2 against the comparator induction agent, thiopental followed by succinylcholine (sux) and isoflurane - N_2O-O_2.

Methods:

Seventy patients ASA I-III were randomly assigned in an open study to one of three groups: A) propofol, high dose (Prop Hi); B) propofol, low dose (Prop Lo) and C) thiopental, followed by sux-isoflurane. Every patient received N_2O-O_2 endotracheal anesthesia and vecuronium if needed during maintenance. Permission was received from the Internal Review Board and informed consent from each patient. Patients were admitted to the study if surgery was expected to be 2 or more hours. Propofol was in aqueous emulsion, 10 mg/ml.

All patients were premedicated with morphine and lactated Ringer's initiated in a large bore vein. All patients received fentanyl 1.5 mcg/kg 3 min prior to induction and glycopyrrolate 0.2 mg. Group A received a 2-2.5 mg/kg bolus titrated to clinical response followed by an infusion in mg/kg/min of 0.2 for 15 min, 0.15 for 15 min followed by a variable rate of 0.1 - 0.15. Group B received 1.0 mg/kg bolus followed by an infusion for 10 min in mg/kg/min of 0.2, 0.15, 0.10 followed by 0.05; this rate was changed to correspond to clinical need. Group C received thiopental 3.0 - 5.0 mg/kg - sux followed by 1.0 MAC ± 10% isoflurane - N_2O.

Upon completion of induction with Prop Hi or Lo, intubation was attempted; half the induction dose or more was administered if intubation was prolonged, the cords closed or difficulty ensued. In group C, after sux, intubation was attempted similarly. A subjective/objective criteria score was recorded by one investigator (J.J.J.) who intubated all 70 patients. These criteria included jaw relaxation, bucking, movement, vocal cord relaxation, duration of intubation and number of attempts. Total points possible was 20; the greater the score the easier and more efficient, the intubation. A force transducer (BioMeter Myograph) and accelerometer were used to objectively judge relaxation at the myoneural junction at intubation and during anesthesia before and after paralysis. The amount of vecuronium per case was averaged. Statistical analysis included T tests, chi square and analysis of variance.

Results

See Table 1 for demography and results. More vecuronium was used with Groups A and B than C ($p < 0.05$). Thirty six % of patients were intubated with propofol only vs. 100% with succinylcholine ($p < 0.05$). Figure 1 shows the total muscle relaxation score at intubation. Group C (succinylcholine had a relaxation score of 17.5 ± 0.3, Group B. 9.7 ± 0.9 and Group A, 9.3 ± 0.7. A difference existed between C compared with A and B ($p < 0.05$). No muscle relaxation was recorded on the force transducer, or accelerometer during periods of no muscular relaxation compared with the awake control.

Discussion:

We found no muscle relaxation difference existed between Hi dose and Lo dose propofol at intubation or afterwards. However, succinylcholine provided significantly more predictable muscle relaxation at intubation. Propofol was associated with more vecuronium use than Group C. We conclude that propofol has poor muscle relaxation properties and its post-induction use as an intubation agent is not advised.

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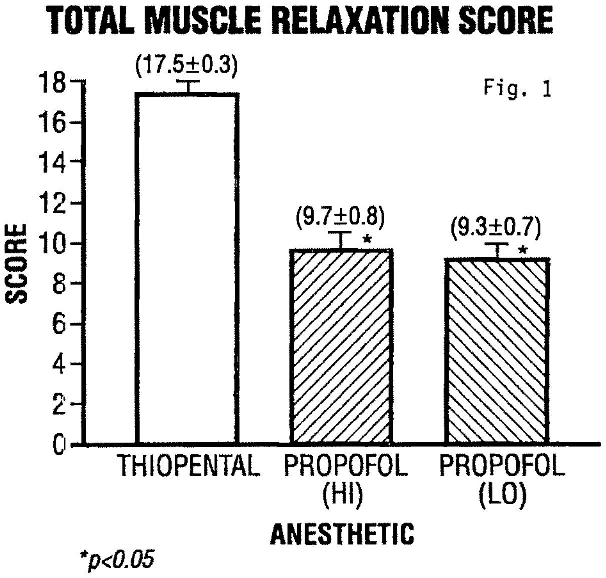

Fig. 1

TABLE 1
DEMOGRAPHY (MEAN ± SE)

	TYPE OF SURGERY Ortho-pedic	Hernia repair	Intra-Abd.	ENT	Age (yrs)	Weight (kg)
PROP HI A (N=24)	14	1	7	2	50 ± 3	80 ± 2
PROP LO B (N=23)	12	5	3	3	52 ± 3	85 ± 4
THIO CONTROL (N=23)	12	6	4	1	52 ± 4	79 ± 3

RESULTS (MEAN ± SE)

Grp.	Durat. Anesth. (min)	Induct. Dose (mg)	Total Dose (mg)	Vecuronium mcg/kg/min	Intub. minus sux
A	185 ± 16	257 ± 16	1891 ± 150	0.61 ± .07	10(42%)‡
B	178 ± 21	160 ± 6*	1693 ± 155	0.62 ± .09	7(30%)‡
C	160 ± 21	372 ± 17	-0-	0.36 ± .06*	- *

‡ A + B = 36% * p < 0.05

TITLE: HEMODYNAMIC VARIABLES AND HISTAMINE LEVELS AFTER DESMOPRESSIN ACETATE ADMINISTRATION IN PATIENTS FOLLOWING CARDIOPULMONARY BYPASS

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INTRODUCTION: Desmopressin acetate (DDAVP) is known to reduce early postoperative blood loss and transfusion requirements in post-cardiopulmonary bypass (CPB) patients (1). DDAVP is also known to produce hypotension and facial flushing (2,3,4). The hemodynamic effects of DDAVP post-CPB after rapid intravenous (IV) infusion have been shown to result in hypotension due to a decrease in systemic vascular resistance (4). Histamine is known to cause hypotension and facial flushing secondary to vasodilation, and this response varies with blood histamine levels. This study measures histamine levels and the acute hemodynamic effects of DDAVP administration post-CPB in randomly assigned patients given rapid or slow IV infusion of DDAVP.

METHODS: After IRB approval and patient consent, sixteen ASA 3 patients, undergoing either coronary artery bypass grafting or heart valve replacement were studied. The patients were randomized into two groups: group 1 received DDAVP (0.3ug/kg) by rapid IV administation over 5 seconds, and group 2 received DDAVP (0.3ug/kg) by slow IV infusion over 5 minutes (in a 100ml D5W infusion), both into a peripheral vein. Patients received a fentanyl (50ug/kg), midazolam (.25ug/kg), pancuronium anesthetic. Only those post-CPB patients were studied, who were hemodynamically stable without inotropic or vasoconstrictor support, on no IV volume infusion or other recent drug administration. A hemodynamic profile was then obtained (baseline), which consisted of cardiac index (CI), systemic vascular resistance index (SVRI), mean arterial pressure (MAP), heart rate (HR), mean capillary wedge pressure (PCWP), and mean central venous pressure (CVP). Arterial blood samples were obtained for histamine level determination. Cardiac output was determined in triplicate, using thermodilution technique with 10 ml of 2° C saline. At 10 minutes after protamine reversal of heparin, DDAVP was administered either IV rapidly, or slowly over 5 minutes by infusion. Hemodynamic profiles were obtained two and fifteen minutes after the DDAVP was administered. Arterial blood samples were drawn at baseline, 3, 5, and 15 minutes after the DDAVP was administered. If the mean arterial pressure was less than 60 mm Hg following DDAVP administration, the blood pressure was treated with phenylephine. The duration of the treated hypotension was noted, and whether or not phenylephine was effective. Arterial histamine levels were measured by radioimmunoassay in duplicate. Between group differences in hemodynamics and histamine levels were tested using repeated measures analysis of variance (ANOVA). Within group changes over time were tested using the Wilcoxon signed pairs rank sum test with each patient as his/her control. A $p<0.05$ was necessary to achieve significance.

RESULTS: There were 8 patients in each group (TABLE I). There were no significant baseline differences between groups 1 and 2. When comparing groups 1 and 2 from baseline to 2 and 15 minutes post DDAVP administration, there were no significant differences in any hemodynamic variables. When analyzing groups 1 and 2 separately, and comparing baseline to 2 minutes post DDAVP administration, there was a significant fall in MAP and SVRI. When analyzing groups 1 and 2 separately, and comparing baseline to 15 minutes post DDAVP administration, the values all returned to baseline level, except CVP, which increased 1.8 mm Hg (clinically insignificant). In group 1, phenylephrine was required in 7 of 8 patients after completion of DDAVP administration. A phenylephrine infusion was started from 2 to 4 minutes and finished from 3 to 14 minutes. In group 2, 5 of 8 patients required phenylephrine infusion, starting from 2 to 3 minutes after DDAVP infusion, and finishing from 4 to 5 minutes thereafter. Histamine levels remained unchanged throughout the period of infusion for both groups together and separately (TABLE II).

DISCUSSION: Antidiuretic hormone (ADH) affects V1 and V2 receptors; V1 mediates the effects of ADH on smooth muscle, and V2 mediates antiduretic effects on the kidney, vasodilation, and release of von Willebrand's and factor XIIIc (3). DDAVP, a congener of ADH, is a V2 specific agonist. Hence hypotension may be expected from DDAVP, secondary to vasodilation. Our results indicate that DDAVP induced vasodilation can cause hypotension, regardless of infusion method. Phenylephrine treated the hypotension successfully in 12 of 16 patients who required treatment. The duration of the hypotension averaged 6 minutes and began about 2 minutes after DDAVP administration was completed. Increased histamine levels were not observed, and thus do not mediate the observed vasodilation. Direct V2 receptor agonism by DDAVP is probably responsible. In conclusion, DDAVP (0.3ug/kg), when administered rapidly IV or slowly over 5 minutes by infusion in otherwise hemodynamically stable patients post-CPB, can cause significant hypotension by decreasing SVRI.

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TABLE I: Hemodynamics

	MAP (mmHG)	SVRI (dynes/sec m2)	HR	CI (L/min.m2)	PCWP (mmHG)	CVP (mmHg)
Group 1 (N=8)						
Baseline(±SD)	69±5	1616±262	79±21	3.0±.5	11.0±5.2	9.3±1.8
2 min(±SD)	52±8*	1073±199*	85±16	3.3±.7	11.6±4.5	9.4±2.2
15 min(±SD)	72±10#	1476±393#	85±10	3.4±.6	11.6±4.0	11.1±2.7#@
Group 2 (N=8)						
Baseline(±SD)	79±20	1850±541	87±20	3.0±.8	11.1±4.7	8.6±4.0
2 min(±SD)	55±8*	1144±214*	93±12	3.3±.6	9.9±4.0	8.8±4.7
15 min(±SD)	82±27	1849±375	86±6	3.0±.6	12.8±3.6	11.8±5.8

*P<0.05, Wilcoxon signed-pairs rank sum test comparing baseline and 2 minutes
#p<0.05, Wilcoxon signed-pairs rank sum test comparing 2 and 15 minutes
@p<0.05, Wilcoxon signed-pairs rank sum test compaimg 15 minutes and baseline

TABLE II: Histamine levels

	Baseline(±SD)	3 minutes(±SD)	5 minutes(±SD)	15 minutes(±SD)
Group 1(ng/ml)	0.8+0.6	0.8+0.5	0.9+0.5	1.5+1.5
Group 2(ng/ml)	0.7+0.5	1.0+0.3	1.2+0.7	1.6+0.9(N=4)

TITLE: DOES EPIDURAL MORPHINE PREDISPOSE TO HERPES SIMPLEX IN CANCER PATIENTS? A COMPARISON WITH EPIDURAL LIDOCAINE.

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INTRODUCTION: In addition to the common complications of epidural morphine such as pruritis, nausea, urinary retention, ventilatory depression and sedation, there are several recent reports suggesting an increased incidence of herpes simplex type I (HS-1) infection in obstetrical patients.[1,2,3] Since immunocompromised cancer patients often receive epidural morphine for pain relief, they also might be at increased risk for HS-1 infection. In order to address this question, we initiated the present study to prospectively examine the incidence of HS-I infection, and other side effects, in cancer patients receiving epidural analgesia with morphine; a cohort group of patients receiving only epidural lidocaine analgesia served as controls.

METHODS: The subjects were 35 informed, consenting cancer patients studied over a 9 month period. The protocol was approved by our IRB. Entry into the study was based on the presence of inadequate pain relief or excessive side effects from oral opioid therapy. All patients had complete medical, neurological and neuroradiological examination (CT scan, MRI, myelogram) to define the patency of their epidural space and to rule out any epidural metastases. No patient was studied if there was a recent history of MI, CHF, systemic infection, bleeding tendency, deranged hepatic function or neurological disorder. No patient had a history of herpes simplex in the past.

Epidural catheters were placed under fluoroscopic control with contrast enhancement. 19 patients with symptoms of sympathetically-mediated pain received a continuous epidural infusion of 1% lidocaine in combination with systemic opioids, as needed. The remaining patients, who had pain predominantly of somatic origin, received epidural morphine as needed for analgesia (Table 1). All patients were monitored daily for any side effect related to epidural analgesia. Those who developed fever or any other sign of infection had a full work up, including multiple cultures both of blood and of the epidural insertion site. All catheter tips were sent for culture and sensitivity at the time of removal. Dermatological consultation was obtained for any skin manifestations suggestive of HS-1 infection.

RESULTS: The study groups are summarized in Table 2. Both were similar with regard to patient age, ASA physical status, sex distribution, narcotic requirement and duration of epidural analgesia. Table 3 summarizes our findings. As expected, there was a higher incidence of pruritis, nausea and vomiting in the morphine-treated group; conversely, lower extremity weakness, hypotension and urinary retention developed only in the lidocaine group. There was no difference between the groups with regard to infectious complications, particularly those associated with HS-1.

DISCUSSION: In this study of cancer pain patients, we found no unexpected side effects related either to epidural morphine or to epidural lidocaine. Furthermore, we found no difference in infectious complications between these treatment modalities, particularly with regard to HS-1 infection. While it is theoretically possible that immunocompromised cancer patients might be more susceptible to infection than obstetrical patients, these data suggest that there is no reason to withhold epidural morphine from cancer patients who cannot obtain adequate pain relief with systemic opioids.

TABLE 1: Daily dose of epidural morphine

Dose	# patients
5-10 mg	3
11-20 mg	4
21-39 mg	4
40-50 mg	2
51-75 mg	3

TABLE 2: Demographic Data

Epidural Medication	# Pt	Age	Pre-Epidural Morphine mg/day	Male/ Female	Duration of Infusion (Days)
Lidocaine	19	32-67	150-300	10/9	8-16
Morphine	16	38-69	150-400	9/7	7-14

TABLE 3: Side effects and complications

	Morphine n=16	Lidocaine n=19
Nausea	1	-
Vomiting	1	-
Itching	2	-
Hypotension	-	1
Sedation	3	2
Motor Weakness	-	1
Migration of catheter	1	-
Cold Sore	1	2
Fever	4	2
Changes in sensorium	-	1
Skin changes at insertion site	3	2
Urinary retention	-	1

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TITLE: HYPOGASTRIC PLEXUS BLOCK: A NEW TECHNIQUE FOR TREATMENT OF PERINEAL PAIN.

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INTRODUCTION: Pelvic pathology may cause severe perineal pain syndromes that are refractory to systemic analgesics. While epidural or subarachnoid blocks may alleviate perineal pain, they are associated with loss of sphincter tone and/or paresis of the lower extremities. In order to avoid these problems, we have devised a method for blockade of the hypogastric plexus. We report here our experience with this technique for the treatment of patients with cancer-related perineal pain.

METHODS: The subjects were 9 informed, consenting male and female patients, ages 45-79 years, with extensive pelvic neoplasia and intractable perineal pain unsuccessfully controlled by systemic analgesics. All patients had a complete neurological examinations and a recent radiological evaluation to define the extent of their cancer.

Patients were placed in the prone position on a fluoroscopy table. A 6" 22 gauge needle was directed mediad and caudad from the lower lateral border of L-4 until the tip was located anterior to the sacral promontory as determined by lateral and A-P X-ray and confirmed by contrast injection (Figures 1 and 2). Diagnostic blockade was performed using 15 ml of 1% lidocaine solution injected slowly. Neurolytic blockade was performed with 5 ml of 6% phenol in water. Patients were then turned to the supine position and observed for any untoward side-effects for 2 hours. Pain relief was assessed using a visual analogue scale from 0-100%.

RESULTS: Moderate (50-80%) to complete (>80%) pain relief was obtained in all patients. Diagnostic blocks lasted for 24-48 hours. 2 patients who underwent neurolytic blockade obtained moderate pain relief for 2 months. No hemodynamic change or alteration in bladder/bowel function was observed and no other adverse effect occurred.

DISCUSSION/CONCLUSIONS: We have found that hypogastric plexus block is a viable option for treating perineal pain secondary to pelvic malignancy. The reduction in pain with local anesthetics indicates that neurolytic blockade should prove effective in producing longer-term analgesia. This has been the case in the 2 patients who have received neurolytic blocks thus far. Further evaluation of this procedure is on-going at this time.

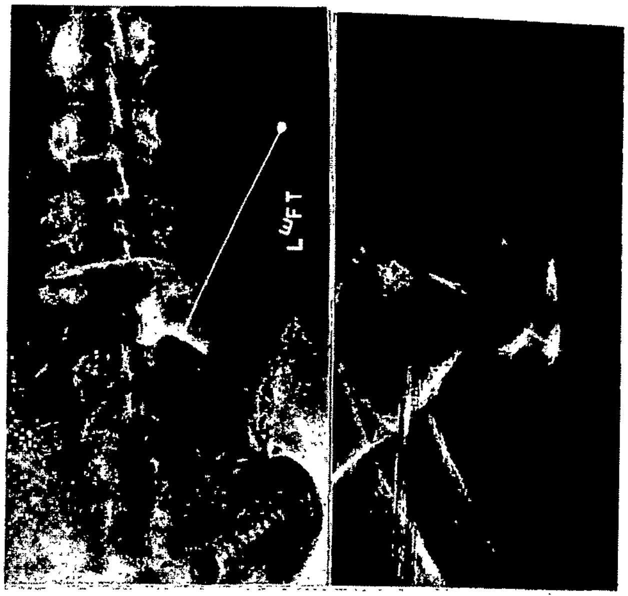
FIGURE 1: AP VIEW
FIGURE 2: LATERAL VIEW

Figures 1 & 2: AP and lateral X-rays showing proper needle-tip placement for hypogastric nerve block confirmed by injection of contrast medium.

TITLE: **ELECTRICAL ACTIVITY ON CARDIOPULMONARY BYPASS IS NOT ASSOCIATED WITH MYOCARDIAL INFARCTION**

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AFFILIATION: **Department of Anesthesiology, Loyola University Medical Center, Maywood, IL**

INTRODUCTION: During aortocoronary bypass surgery (ACB), the greatest damage to the myocardium is thought to be during cardiopulmonary bypass (CPB). The myocardial fraction of creatine kinase (CK-MB) determined after termination of CPB is a measure of myocardial injury. In order to minimize the myocardial damage, it is necessary to identify its correlates during CPB.

In a study of 20 patients, Lockerman et al.(1) reported that the period of reperfusion ventricular fibrillation at the end of CPB had a correlation coefficient of 0.75 with CK-MB. In their study, the fibrillation was terminated by electrical defibrillation. The aim of this study is to verify this finding and identify other variables that will correlate with CK-MB measured post-operatively.

In the presence of coronary stenoses, the myocardium has a great propensity to develop subendocardial ischemia during ventricular fibrillation and other arrhythmias. Hence the duration of ventricular fibrillation may be related to CK-MB. If the myocardium is ischemic, it may have a greater propensity towards ventricular fibrillation during the initial period of reperfusion.

Patients with critical coronary stenoses who are administered antegrade cardioplegia during CPB may have inadequate myocardial protection leading to greater ischemic damage during CPB. These patients are also more likely to have suffered greater ischemic damage in the period before CPB. Thus, the patients with critical stenoses may have higher CK-MB than the patients with non-critical stenoses.

METHODS: After Institutional Review Board approval, informed consent was obtained from 52 patients for aortocoronary bypass surgery. Systemic hypothermia to 28°C, and topical hypothermia with iced saline were used. Antegrade cold potassium cardioplegia was administered every 20 minutes. The measured myocardial temperature was maintained below 15°C.

The coronary angiograms were studied to determine the total number of vessels with stenoses greater than 70% and critical stenoses greater than 90%.

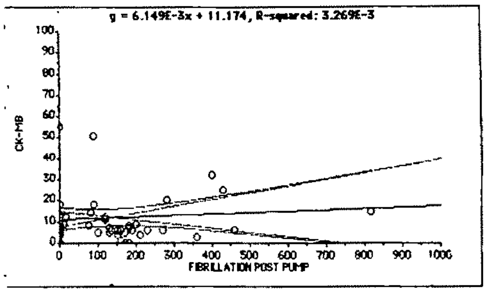
Intraoperatively, all patients were monitored with Marquette 8500^R Holter monitor which recorded ECG leads I, III and modified CM_5 which had positive electrode at V_5 and the negative electrode just below the right clavicle in the mid-clavicular line. Full disclosure of all the ECG's recorded on the Holter was obtained. This was used to measure the periods of fibrillation pre- and post-bypass, the period of non-fibrillatory electrical activity and electrical quiescence on bypass, and the total number of defibrillations.

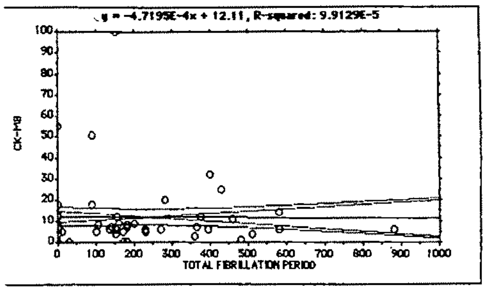
CK-MB values were obtained immediately post-surgery (CK-MB1) and on the morning after surgery (CK-MB2). CK values were measured spectrophotometrically. CK-MB was determined by immuno-inhibition.

RESULTS: The Pearson correlation coefficients of the duration of CPB, the duration of electrical activity during cardioplegia, the duration of fibrillation on pump and the number of defibrillations required after CPB to establish a rhythm with CK-MB1 and CK-MB2 are -0.192, 0.314; -0.025, 0.071; -0.026, 0.250; 0.026, 0.302 respectively. Eight and 2 patients had CK-MB1 and CK-MB2 greater than 5% of the respective CK value. No difference is the measured variables was found between these and the remaining patient.

Thirty eight patients had one or more coronaries with greater than or equal to 90% stenosis. The correlation coefficients between the number of coronaries with critical stenoses and duration of ventricular fibrillation on pump, the duration of electrical activity during cardioplegia, the number of defibrillations required after CPB to establish a rhythm, CK-MB1 and CK-MB2 are 0.279, -0.049, -0.199, 0.053, -0.165 respectively.

The scattergrams of CK-MB1 versus the period of fibrillation post pump and the total fibrillation period presented below show the linear regression line, the confidence limits for the slope of the regression line and the confidence bands for the true mean of the CK-MB value.





DISCUSSION: Our results are substantially different from those of Lockerman et al.[1] Since the reperfusion ventricular fibrillation is not self terminating but is promptly terminated by electrical defibrillation, the duration of fibrillation may not be a marker for ischemia and hence CK-MB release.

None of the studied variables correlated with CK-MB and hence they can't be used as measures of myocardial damage during CPB. The number of coronaries with critical stenosis does not correlate with intra-operative electrical activity or post-operative CK-MB. Thus patients with greater coronary stenoses do not appear to be at a greater risk for perioperative infarction.

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TITLE: INCIDENCE OF MYOCARDIAL ISCHEMIA ON ARRIVAL FOR AORTOCORONARY BYPASS SURGERY

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INTRODUCTION: Using 2-lead Holter monitoring, Knight et al.(1) found none of their 50 patients had myocardial ischemia on arrival for aortocoronary bypass surgery. Two patients developed ischemia during insertion of central venous or pulmonary artery catheter. Slogoff and Keats(2) found ischemia in 122 out of 444 patients in leads II and/or V_5 recorded on the operating room monitor. Both studies used 100 mcV ST deviation as the criterion for ischemia. There is a significant difference between the two results. If the latter incidence is correct, aggressive management of ischemia in these patients may be warranted. The aim of this study was to determine the incidence of ischemia by using modified 12-lead digital electrocardiograms (ECG) analyzed by multiple methods.

METHODS: After Institutional Review Board approval, informed consent was obtained from 64 patients. Marquette MAC-12^R digital electrocardiograph was used to acquire ECG. It has a frequency response of 0.05-100 Hz, common mode rejection ratio >130dB and digital line frequency and baseline roll filters. For each ECG recorded, a median ECG complex is determined and the measurements are acquired on this complex thus reducing the effect of beat-to-beat variability. Marquette MUSE^R system implemented on a PDP 11/73 computer was used to acquire a number of measurements on the ECG. Limb leads, V_4, V_5 and V_4', V_5' - one interspace below V_4, V_5 were recorded prior to the placement of invasive monitoring catheters in 29 patients scheduled in the morning and prior to the start of anesthetic induction in 33 patients scheduled in the afternoon, who had their catheter placement completed 30 to 60 minutes prior to arrival in the operating room. Patients scheduled in the morning were often sicker than those scheduled in the afternoon. Measurement and analysis by computer was verified by observers including a cardiologist.

Ischemia was detected by a number of methods. For the sake of simplicity, results of 11 methods are presented here. The first 8 methods are based on all leads. The first method is based on any one lead having greater than 100 mcV ST deviation. The second method is based on any one lead having greater than 50 mcV ST deviation. The third method identifies if any lead has an inverted T wave of amplitude greater than 100 mcV, accompanied by at least 50 mcV ST deviation in the same lead. Alternatively, if T wave inversion is present in 2 or more of the inferior leads II, III and aVF or 2 or more of lateral leads V_4, V_5, V_4', V_5', I and aVL then also ischemia is considered to be present. The fourth method considers an ECG to be ischemic if the QRS complex in the frontal plane is most positive in lead I and the T amplitude in lead III is greater than the T amplitude in lead I. The fifth method considers ischemia to be present if the septal q wave is absent in lead V_5. The sixth method is a combination of the first and the third, the seventh is a combination of the second and the third and the eighth is a combination of second through fifth methods. The ninth method is based on 100 mcV ST deviation in II and V_5, the tenth on 100 mcV ST deviation and significant T wave inversion in II and V_5. The eleventh method is based on 50 mcV ST deviation and significant T wave inversion in Leads II and V_5.

For longer term monitoring, Marquette 8500^R Holter monitor was used to record modified CM_5 lead with the positive electrode at V_5 and the negative electrode below the right clavicle in the midclavicular line. Leads I and III were also monitored. The Holter monitor has a frequency response of 0.05 - 80 Hz and common mode rejection > 60 dB. High resolution ST segment trend plots were obtained from the Holter tapes by Marquette 8000^R Holter analysis system. A 100 mcV further ST depression from the baseline was considered to represent ischemia.

RESULTS: The percentage of patients with ischemia detected by each method for 12-lead ECG is listed in Table I.

TABLE I: PERCENTAGE OF ISCHEMIC PATIENTS

METHODS	#	1	2	3	4	5	6	7	8	9	10	11
AM	#	6	16	21	5	18	21	25	28	3	12	17
PATIENTS	%	21	55	72	17	62	72	86	97	10	41	59
PM	#	6	13	19	0	23	21	24	32	1	13	16
PATIENTS	%	18	39	58	0	70	64	73	97	3	39	48

One patient who had ischemia by the ninth method had a new 100 mcV ST deviation on the Holter monitor, the second had less than 100 mcV ST deviation on the Holter monitor while the third did not have a Holter monitor. The lone patient with catheter who had ischemia by the ninth method had a new 100 mcV ST deviation on Holter monitor also.

DISCUSSION: The divergent results obtained by the 11 methods indicate that methodology plays a crucial role in the detection of ischemia. Which of these methods may prove to be useful in the various clinical situations remains to be determined.

The ninth method is similar to that of Slogoff and Keats(2). Knight et al.(1) used the criterion of a new 100 mcV ST deviation compared to a baseline period on the Holter recording. Our results are in general agreement with those of Knight et al.(1).

The specificity of our 12-lead methods may be reduced by persistent ECG changes whose effects can be measured from an ECG recorded when the patient is not ischemic. Lack of ischemia can not be determined from symptoms. One strategy is to obtain recordings over prolonged period thus increasing the likelyhood that part of this period was free from ischemia(1).

By using more leads and features, the sensitivity for ischemia detection is substantially increased while the specificity is presumably reduced. During monitoring, if the hemodynamics is stable, high sensitivity maybe preferable as the adverse effects of therapy for ischemia can often be limited in a monitored situation.

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TITLE: HIGH-VOLUME FENTANYL COMPARED WITH OTHER NARCOTICS AFTER CESAREAN SECTION:
ANALGESIA AND RESPIRATORY STATUS

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Introduction. A single epidural dose of fentanyl, which is safe and efficacious for analgesia after cesarean section, is limited by a short duration of action (1). Alternative methods of administering fentanyl include continuous infusion and increased volume of diluent (2). This study examined analgesia and side effects, in particular respiratory status, with epidural fentanyl with a large volume of diluent (20 ml compared with 10 ml) with or without continuous infusion; with epidural hydromorphone and morphine; and with parenteral morphine.

Methods. All patients gave informed consent to the study as approved by the institutional review board. At the end of elective cesarean section with lumbar epidural anesthesia (2% lidocaine; 1:200,000 epinephrine), 67 patients were assigned randomly to receive an epidural bolus of fentanyl, 75 µg in 10 (FB/10) or 20 (FB/20) ml sodium chloride (NaCl) or a bolus with an 8-hr continuous infusion, 7.5 µg/ml at 10 ml/ hr (FCI/10) or 2.5 µg/ml at 20 ml/hr (FCI/20); epidural hydromorphone, 1 mg (EH), or epidural morphine, 5 mg (EM), the latter two agents in 10 ml with NaCl; or parenteral morphine (PM). Patients were monitored in the recovery room for 10 hr, during which pain was measured with a 10-cm visual linear analog scale on arrival to the recovery room and every 30 min thereafter. Respiratory rate (RR), blood pressure, heart rate, oxygen saturation (SaO_2), and end-tidal carbon dioxide ($PetCO_2$) were measured simultaneously. The incidences of pruritus and nausea were recorded. Additional analgesia included 75 µg in 10 or 20 ml for FB patients and 50 µg in 10 or 20 ml in FCI patients (maximal, 2 doses for both groups) and iv and im doses in the PM patients; EH and EM groups did not receive additional analgesia. Data were analyzed by Kruskal-Wallis for analysis of variance (ANOVA) and Wilcoxon ranked sum tests ($P < 0.0024$).

Results. Time to first analgesic was shorter with FB/10 and PM and longer with EM than in all other groups (Table 1). Incidence of pruritus was higher with FB/10 and EH than with the other analgesics. Mean SaO_2 or % of patients who had $SaO_2 < 95\%$ and mean $PetCO_2$ or % of patients with $PetCO_2 > 35$ mm Hg did not differ statistically between the groups, nor did pain score, nausea, vomiting, or sedation. No patients had a respiratory rate < 10 breaths/min.

Discussion. In this study, as shown previously (2), with a single bolus of epidural fentanyl, a high volume of diluent resulted in a longer duration of action than did a smaller volume of diluent. Also, the high volume of continuous infusion of epidural fentanyl, despite the smaller dose, tended to have a longer duration of action than did the smaller volume. Because fentanyl is highly lipid soluble, a high-volume, continuous epidural infusion of fentanyl is effective and safe after cesarean section and enables duration of analgesia to be varied as needed. Although no overt respiratory depression was detected in the small number of patients we studied, extensive clinical monitoring and close observation demonstrated, especially with the less lipid soluble narcotics, subtle changes in SaO_2 and $PetCO_2$ that may be useful in monitoring for signs of respiratory depression.

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Table 1. Comparison of Effects of Epidural Fentanyl with Other Narcotics on Analgesia and Respiratory Status of Women after Elective Cesarean Section

(continuation of Table 1)

		Morphine		Epidural Fentanyl Bolus		Epidural Fentanyl Infusion	
	Epidural Hydromorphone	Epidural	Parenteral	10 ml	20 ml	10 ml/hr (75 µg/hr)	20 ml/hr (50 µg/hr)
Number of patients	9	10	8	10	10	10	10
Time to first analgesia (hr)	14.1 ± 7.7	21.4 ± 4.9*	1.89 ± 0.8†	3.13 ± 8.64†	5.68 ± 2.72	7.14 ± 4.57	9.48 ± 4.6
SaO_2 (%)							
Mean	96.5 ± 1.2	96.5 ± 1.4	95.9 ± 1.5	97.21 ± 1.2	96.4 ± 1.3	96.14 ± 0.8	97.3 ± 0.7
Range	90 - 100	91 - 100	89 - 100	93 - 100	90 - 100	92 - 100	90 - 100
$SaO_2 < 95\%$ (% of patients)	67	40	88	30	50	60	20
$PetCO_2$ (mm Hg)							
Mean	32.9 ± 5.0	29.5 ± 4.0	29.4 ± 4.6	29.4 ± 2.6	29.4 ± 3.4	29.9 ± 3.9	27 ± 2.7
Range	23 - 44	15 - 39	16 - 37	23 - 37	16 - 38	21 - 38	16 - 34
$PetCO_2 > 35$ mm Hg (% of patients)	55	40	25	0	10	20	10

SaO_2: arterial oxygen saturation.
$PetCO_2$: end-tidal carbon dioxide.

*$P < 0.0009$ compared with other analgesic groups.
†$P < 0.003$ compared with other analgesic groups.

TITLE: "COMPARISON OF ONSET TIME BETWEEN BUPIVACAINE 0.5% AND 2-CHLOROPROCAINE 3% WITH AND WITHOUT FENTANYL 75 mcg"

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INTRODUCTION: The authors have observed that the addition of fentanyl to bupivacaine during epidural anesthesia, significantly reduced the onset time for T4 sensory blockade for cesarean section (C/S).[1,2] We chose to test the hypothesis that the addition of fentanyl 75 mcg to bupivacaine 0.5% (bupiv 0.5%) would reduce the onset time for surgical anesthesia for C/S to equal the onset time of 2-chloroprocaine 3% (2-CP 3%).

METHODS: The study was approved by the human studies committee and informed consent was obtained from each patient. The study was conducted in a randomized double-blind fashion. The same blinded observer performed sensory testing using pain to pinprick at 1-2 minute intervals on all patients. Twenty-eight ASA I patients scheduled for elective cesarean section had epidural catheters placed. Group 1 (n1=7) received bupiv 0.5%; group 2 (n2=7) received bupiv 0.5% plus fentanyl 75 mcg; group 3 (n3=7) recieved 2-CP 3%; and group 4 (n4=7) recieved 2-CP 3% plus fentanyl 75 mcg. Patients were positioned with the left side down and epidural catheters were placed at L2-3 or L3-4 and threaded 3-4cm cephlad (there were no dural punctures). Patients were pre-hydrated with LR 30ml/kg. A test dose of lidocaine 1% + epinephrine 1:200,000 3ml was administered to each patient. Drug dosages for bupiv 0.5% and 2-CP 3% were calculated based on the patients height (5'0"-5'4" recieved 15ml, 5'5"-5'-9" recieved 20ml). The local anesthetics were administered at 5ml/min until the calculated dose given. Fentanyl 75mcg (groups 2 & 4) was administered with the first 5ml of local anesthetic. Patients were monitored with ECG, pulse oximetry, and automatic blood pressure cuff set at 2 minute cycling interval. Hypotension was defined as a systolic BP less than 100mmHg and was treated with fluids and ephedrine 5mg p.r.n..

STATISTICAL ANALYSIS: Testing for statistical significance was done using two factor analysis of variance follwed by Newman-Keul's multiple sample comparsion testing.

RESULTS: There were no adverse affects on the neonate or clinically significant changes in maternal hemodynamics. The maternal age, height, weight, and bupiv or 2-CP dose did not differ significantly between groups 1 to 4 (p>0.05). In group 1 the mean time for sensory blockade at T4 was 19.3 +/- 4.9 minutes and for group 2 was 12.7 +/- 2.0 minutes (p<0.005, table 1). Two-factor analysis of variance (ANOVA) between groups 1 and 2 showed a significant difference at p<0.0001 (representing a 35% reduction of mean onset time). The coefficient of variation of the mean onset times for group 1 subjects compared to group 2 subjects demonstrated a 50% reduction in between-subject variation (p<0.001). In group 3 the mean time for sensory blockade at T4 was 12.7 +/- 3.6 minutes and for group 4 was 12.3 +/- 2.9 minutes (p>0.05, table 1). Two-factor ANOVA between groups 3 and 4 showed no significant difference (p>0.05). Two-factor ANOVA of the mean onset time for T4 sensory blockade between groups 2, 3,and 4 showed no significant difference (p>0.05, table 1).

DISCUSSION: The study demonstrates that the addition of fentanyl is statistically and clinically significant at reducing the analgesic onset time for cesarean section when combined with bupivacaine 0.5% (35% reduction). The addition of fentanyl to 2-chloroprocaine 3% did not change the T4 anesthetic onset time when compared to 2-CP 3% alone. The T4 anesthetic onset time of the fentanyl/bupivacaine mixture is equal that of 2-chloroprocaine 3% with or without added fentanyl. This demonstrates that the addition of fentanyl to bupivacaine has a potentiating effect which is absent with 2-CP 3%. Studies have demonstrated that 2-CP reduces the duration of analgesia produced by epidural narcotics after cesarean section.[3,4] Our study demonstrates that the T4 surgical analgesic onset time for C/S of bupiv 0.5% can be reduced to that of 2-CP 3% by adding fentanyl to bupiv 0.5%. Thus, one can benefit from a rapid onset equal to 2-CP 3% without the reduction in duration of analgesia of epidural narcotics. The mechanism by which fentanyl potentiates bupiv 0.5% is unclear and further studies need to be performed.

TABLE 1. ONSET OF SENSORY BLOCKADE

	T7 (MIN)	T6 (MIN)	T5 (MIN)	T4 (MIN)
BUPIVACAINE	13.1+/-3.8	15.0+/-4.0	16.9+/-4.3	19.3+/-4.5
BUPIVACAINE + FENTANYL	8.1+/-0.9	9.9+/-1.1	11.3+/-1.5	12.7+/-2.0
P-VALUE	<0.05	<0.025	<0.025	<0.005
% REDUCTION	38	34	33	34
2-CHLOROPRO.	9.0+/-3.1	10+/-3.9	11.3+/-3.1	12.7+/-3.6
2-CHLOROPRO. + FENTANYL	8.6+/-2.1	9.7+/-2.4	11.0+/-2.6	12.3+/-2.9
P-VALUE	>0.05	>0.05	>0.05	>0.05

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Title: **TYPE AND FREQUENCY OF ARTIFACTS RECORDED ON AUTOMATED ANESTHESIA RECORDS**

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Introduction: Recording artifacts or incorrect information on an automated anesthesia record keeping system has legal implications; most anesthetists are reluctant to use a system that potentially records false information. Knowing the type and frequency of artifacts is the first step to eliminating the incorrect information.

Methods: Twenty-four automatically recorded anesthesia records (ARKIVE® Diatek, San Diego) were recorded during cardiothoracic surgery. These were retrospectively reviewed and the type and incidence of artifacts noted. All *artifact notes* on the record (noted by the anesthetist during the case) were counted in addition to any obvious untagged artifacts. The total number of vital-sign determinations was totaled and the ratio of the number of artifacts to the number of vital-sign determinations calculated. To ascertain the number of vital-sign determinations, those vital-signs recorded every 5 minutes were counted once each 5 minute period and those vital-signs continuously recorded (such as temperature and heart rate) were considered to have one determination each 5-minute period. Artifactual values that continued throughout a 5-minute period were counted as a single artifact. Seven vital-signs were reviewed: heart rate, arterial BP, SpO_2, end-tidal CO_2, temperature, respiratory rate, and EEG spectral edge. Monitors used to determine these included: Hewlett-Packard (HP) EKG, HP arterial blood pressure monitor, Ohmeda 3700 pulse oximeter, POET end-tidal CO_2 monitor, Lifescan processed EEG, and YSI 400 temperature probe. The ARKIVE was configured to print the blood pressure, SpO_2, end-tidal CO_2, respiratory rate, and EEG spectral edge, every five minutes; the heart rate and temperature every one minute.

Results: Twenty-nine artifacts were noted on the twenty-four anesthesia records (see table 1). The number of vital-sign determinations (6049) recorded resulted in an artifact/vital-sign ratio of 1 to 209. The most common variable affected by artifact was HR. No artifactual end-tidal CO_2 or SpO_2 values were noted.

Discussion: The number of artifacts documented was low in relation to the total number of variables recorded on the anesthesia record. Most artifacts recorded by the automated record keeping system originate from the individual monitors producing spurious values; the automated anesthesia record is only as accurate as the monitors attached to it. Many of the noted artifacts could be eliminated with simple algorithms incorporated into either the monitor or automated record keeper's software.

The low incidence of artifacts may be attributable to several causes. One, the ARKIVE uses an averaging algorithm which mimics the way most anesthetists plot manual records. When configured to print in 5 minute intervals (similar to standard records) the system averages all values obtained in the previous 5 minute period: this averaging may hide some artifacts. Second, we configured the ARKIVE to interpret HR from the pulse oximeter and not the EKG as the EKG is prone to electrocautery interference. Third, either while doing the case or in our review we missed subtle artifacts. Many artifacts are easily noted, yet others are disguised. The obvious artifacts include the unnatural drop in temperature when the temperature probe is removed from the patient and the zero-values produced during the warm-up phase of some monitors. An interesting observation is that most artifacts produce artificially elevated values.

In summary, few artifacts were recorded and most of these were obvious. In addition, we speculate that with additional hardware and software modifications, the number of artifacts recorded could be further reduced.

Table 1.

Vital-sign affected, cause, and number of occurrences (n)

HR	Electrocautery interference affecting heart rate determination (1) Incorrect value determined while on CPB (8) Pulse oximeter providing incorrect HR (1)
Temp	Temperature probe not in proper place (6)
BP	ABG draw temporarily affecting BP value (7)
RR	End-tidal CO_2 monitor providing incorrect rates (1)
EEG	Electrocautery interference (5)

TITLE: TRANSNASAL BUTORPHANOL IN THE TREATMENT OF EPISIOTOMY PAIN

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Introduction. The production of effective, clinically safe analgesia continues to be one of the challenges in the management of the postoperative patient. The pharmacokinetic characteristics of butorphanol suggest that the systemic absorption of this drug following application to the nasal mucosa has the potential for producing analgesia consistent with these criteria. The present study evaluated the efficacy and clinical safety of analgesia following the intranasal administration of butorphanol in patients with moderate to severe pain due to episiotomy.

Methods. Approval of the Institutional Review Board and informed patient consent were obtained. Seventy-six healthy female patients experiencing moderate to severe episiotomy pain were enrolled. Patients were randomly assigned to a single dose of 0.25, 0.5, 1 or 2 mg butorphanol tartrate or placebo. Each patient received a metered dose using a nasal spray pump supplied by Bristol-Myers Laboratories. The test medication was administered by a research nurse. Neither the patient nor the observer was aware which medication was being administered. Each patient was interviewed at 0.25, 0.5, 1, 2, 3, 4, 5 and 6 hours after treatment, or until remedication for pain was requested (at or before hour 6). Pulse, blood pressure and respiratory rate were recorded at each interval. During each interview, the patient was asked to evaluate the pain relief using scales for Pain Intensity, Pain Relief, and Pain Half Gone. At the final interview Global Assessments of the treatment by the observer and the patient were obtained. Pain Intensity Differences were calculated. Pain Intensity was evaluated as severe =3, moderate =2, slight =1, or none =0. Pain Relief was rated as complete =4, a lot =3, some =2, a little =1, or none =0. The observer and patient Global Assessments of the test medication were recorded after 6 hours (or prior to remedication). The scale used was excellent =5, very good =4, good =3, fair =2, or poor =1. The time at which additional pain medication was requested and any side effects were recorded.

Results. Patients receiving 1 or 2 mg of butorphanol responded more favorably on several of the analgesic ratings than did patients given placebo. The onset of analgesia was rapid for the butorphanol 2 mg dose. The 2 mg dose was significantly ($p<0.05$) superior to placebo at 30 minutes, and 2 and 4 hours on the Pain Relief scale; at hours 1 and 4 on the Pain Half Gone scale; and at hour 4 on the Pain Intensity Difference scale. The 1 mg dose was significantly better than placebo on the Pain Relief scale at hours 1 and 2, and on the Pain Half Gone scale at 1 hour. The observer rated Global Assessment of treatment was highest with butorphanol, 2 mg, while the patient assessment was highest with 0.5 mg. The 2 mg dose was significantly better than placebo for time to remedication. The 0.5 mg dose showed few differences from placebo, while the 0.25 mg dose did not differ significantly from placebo. The most frequently reported adverse effects, dizziness and somnolence, appeared to be dose-related. There were no clinically significant drug effects on blood pressure or respiratory rate.

Discussion. Transnasal butorphanol, 1 mg or 2 mg was effective in relieving post episiotomy pain. The 2 mg dose was most effective. The primary side effects, dizziness and somnolence, were dose related. The transnasal route of administration for butorphanol appears to be a new alternative worthy of further investigation.

TITLE: A COMPARISON OF ELECTROMYOGRAPHIC RESPONSE AND VISUAL TACTILE RESPONSE TO POSTERIOR TIBIAL NERVE STIMULATION USING VECURONIUM

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Introduction: Vecuronium is a non-depolarizing neuromuscular blocking agent with an intermediate duration of action. It does not cause histamine release or alter hemodynamics and has minimal cumulative properties.

The purpose of this study is to compare electromyographic versus visual plus tactile responses to posterior tibial nerve[1,2] stimulation. The use of the posterior tibial or peroneal nerve stimulation to monitor neuromuscular blockade is useful when monitoring of ulnar nerve or facial nerve is not possible.

Methods: Institutional review board approval was obtained and the study was comprised of 39 patients, 5-66 years of age (mean ± SD:26.5±15.5), 19-108 kg (mean ± SD:61.4±18.2) without neuromuscular disease. The anesthetic technique consisted of nitrous oxide and oxygen (60:40) supplemented with isoflurane. The intubation was achieved with vecuronium 0.1 mg/kg followed either by bolus 0.01-0.02 mg/kg (Group 1) or by infusion 0.8-1.0 ug/kg/min (Group 2) upon the reappearance of T1 during train of four stimulation (T04). The doses were adjusted in order to maintain T1 at approximately 10% of the control. The plantar flexion of the foot was recorded on an EMG unit (Puritan Bennett NMT 221) upon stimulation of the posterior tibial nerve. The infusion was stopped about 10 to 15 minutes prior to the anticipated completion of surgery. The antagonism of the neuromuscular blockade was achieved with atropine and edrophonium.

On the opposite side square wave supramaximal voltage of 200 microseconds duration was delivered from the Digistem II nerve stimulator (Neuro Technology) to the posterior tibial nerve via surface electrodes at 0.5 Hz. The visual and tactile responses during train of four stimulus was evaluated.

Temperature was maintained between 35 to 37°C. The end tidal CO_2 was continuously monitored and maintained between 35 and 40 torr by appropriate ventilatory techniques.

Results: The data was analyzed statistically (mean±SD). The mean time required to obtain 100% suppression (T1%)-EMG/Tactile/Visual was 4.09±1.79/5.10±3.96/5.12±3.95 mins. for Group 1; and 6.10±4.45/7.01±4.20/7.01±4.20 mins. for Group 2. (Table 1) The intubation was achieved in 4.39±1.69 mins. for Group 1; and 5.78±3.87 mins. for Group 2. The mean time to extubation following reversal with edrophonium was 10.60±7.23 mins. with a maximum train of four ratio (TR%) and T1% of 92.90±11.06 and 99.34±28.75, respectively for Group 1; and 15.84±8.92 mins. with a maximum TR% and T1% of 88.70±18.46 and 90.50±26.23, respectively for Group 2. (Table 2) The total vecuronium dose for Group 1 was 9.17±4.86 mg and for Group 2 was 12.79±3.57 mg. (P-value < 0.05)

Conclusion: Posterior tibial nerve can be monitored when other peripheral nerves are not accessible. Even though recovery by visual/tactile and clinical observations were adequate for extubation and transport to the recovery room, the maximum recovery (TR%) with EMG monitor was observed after 36.57±31.53 mins. for Group 1 and 39.83±21.24 mins. for Group 2 upon arrival to the recovery room. All patients were discharged from the recovery room in 60-90 mins.

TABLE I
MAXIMUM TWITCH SUPPRESSION

	Post Tibial Nerve with EMG		Post Tibial Nerve with Digistem II				Intubation Time After Vecuronium	
	Time for Block		Time for Min T		Time for Min V			
	GROUP 1	GROUP 2	GROUP 1	GROUP 2	GROUP 1	GROUP 2	GROUP 1	GROUP 2
Mean	4.09	6.10	5.10	7.01	5.12	7.01	4.39	5.78
SD	±1.79	±4.45	±3.96	±4.20	±3.95	±4.20	±1.69	±3.87
P-Value	<0.05		<0.05		<0.05		<0.05	

TABLE 2
MAXIMUM NEUROMUSCULAR RECOVERY

	Degree of Recovery				Time from Reversal to Extubation		Time from Reversal To Max Recovery	
	T1%		TR%					
	GROUP 1	GROUP 2	GROUP 1	GROUP 2	GROUP 1	GROUP 2	GROUP 1	GROUP 2
Mean	99.34	90.50	92.90	88.70	10.60	15.84	36.57	39.83
SD	±28.75	±26.23	±11.06	±18.46	± 7.23	± 8.92	±31.53	±21.24
P-Value	>0.05		>0.05		>.05		>.05	

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TITLE: ULNAR AND PERONEAL NERVE RESPONSE VERSUS VOCAL CORD RELAXATION

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Introduction: Atracurium besylate[1] is a non depolarizing muscle relaxant with intermediate duration of action. Muscle relaxation for endoscopic examination of the larynx and esophagus is commonly achieved with succinylcholine infusion.

The purpose of this study was to assess the quality of vocal cord relaxation provided with Atracurium and to compare with neuromuscular responses on stimulation of peroneal and ulnar nerve.

Methods: After institutional review board approval, 11 patients, ages 5-58 years and ASA I-III classification were studied. All patients were free of neuromuscular disease. The anesthetic technique consisted of pre-medication with Atropine 0.01 mg/kg IM 1 hour prior to surgery or no pre-medication was given. Induction was achieved with Thiopental 4 mg/kg and Atracurium 0.5 mg/kg used to facilitate intubation at maximum T_1 suppression. The electromyographic response of the adductor pollicis muscle was recorded on a EMG unit (Puritan Bennett NMT 221) following train of four (TO_4) stimulation of the ulnar nerve at the wrist. The muscle relaxation was maintained with Atracurium 5-8 ug/kg/min[2]. The dose was adjusted manually on reappearance of T_1 of TO_4.

Peroneal nerve stimulation was done simultaneously and dorsiflexion of the foot noted by visual and tactile means.

An evaluation of vocal cord relaxation was made by the surgeon through an operating microscope with 10 time magnification and graded as excellent, satisfactory or unsatisfactory.

The temperature was maintained between 35-37°C. The end tidal CO_2 was maintained between 34-40 torr by appropriate ventilatory techniques.

Results: The time taken for maximum suppression of T_1 for ulnar/peroneal was 2'55"/1'40" to 11'40"/15'00" (Table I). The time to intubation following Atracurium bolus was 1'40" to 4'20". The mean duration of anesthesia was 104 mins. The vocal cord relaxation was excellent in all cases. The recovery index (25-75% recovery) for was 4'50". The maximum ulnar nerve recovery after reversal of muscle relaxant was observed to be 5'20" to 22'40" (Table II). Extubation was achieved in 6'00" to 22'40". The extubation was based on neuromuscular and clinical recovery.

Discussion: Atracurium provided excellent relaxation of vocal cords. The recovery time was vocal cord < dorsiflexion < thumb adduction. After intubation with Atracurium 0.5 mg/kg the residual blockade can be reversed within 30 min. if surgery is completed sooner than planned and should the surgery be prolonged the residual blockade can be reversed within 10-15 mins. of discontinuing infusion. On the other hand, prolonged Succinylcholine infusion may produce tachyphylaxis and phase II block, causing problems at recovery.

TABLE I
MAXIMUM TWITCH SUPPRESSION

Case No.	Ulnar Nerve Time For Block	Ulnar Nerve Degree Of Supprn. (%)	Common Peroneal Nerve Time For Block	Common Peroneal Nerve Degree Of Supprn. (%)	Time To Intubation After Atracurium
1	2'55"	100	2'00"	100	1'40"
2	16'00"	76	4'40"	100	3'20"
3	5'20"	100	3'20"	100	3'00"
4	6'20"	100	9'40"	75	4'20"
5	11'40"	75	12'40"	100	9'20"
6	3'40"	100	10'40"	100	3'40"
7	3'20"	100	3'40"	50	-
8	3'40"	100	13'00"	90	4'00"
9	4'00"	100	19'00"	50	5'20"
10	4'10"	100	4'00"	90	5'00"
11	9'00"	93	11'20"	50	9'00"

TABLE II
MAXIMUM NEUROMUSCULAR RECOVERY*

Case No.	Time From Reversal To Recovery	Degree of Recovery T1(%)	Degree of Recovery T4/T1(%)	Time From Reversal To Extubation
1	19'20"	30	16	19'00"
2	17'20"	117	65	18'40"
3	21'40"	54	88	22'40"
4	22'40"	71	31	18'40"
5	17'00"	83	46	6'00"
6	20'40"	81	56	19'40"
7	5'20"	81	73	-
8	4'20"	79	56	1'40"
9	13'20"	65	60	13'00"
10	6'40"	55	97	8'00"
11	15'00"	101	64	23'40"

*ulnar nerve

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TITLE: DERMAL ANESTHESIA IN CHILDREN USING A EUTECTIC MIXTURE OF LIDOCAINE AND PRILOCAINE

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Introduction. Pain associated with venipuncture remains a significant problem in the medical management of the pediatric patient. An emulsion, consisting of the eutectic mixture of lidocaine base and prilocaine base in a dermatologic cream (EMLA), has been reported to penetrate intact skin and produce dermal anesthesia. The efficacy of this combination is attributed to an 80% concentration of local anesthetics, as compared with 20% active drug in single component formulations.(1)

Methods. Following approval by the appropriate Institutional Review Boards, the efficacy and safety of EMLA 5% cream were measured in 96 children, 5 to 12 years of age, requiring venipuncture. A double blind, randomized, placebo controlled design, stratified by age was used. The test medication or placebo was applied to the skin on the dorsum of the hand or the antecubital fossa, covered with an airtight dressing and allowed to remain in place for a minimum of 60 min. Efficacy was measured by the pain response during venipuncture using a 100 mm, visual analog scale where: 0=no pain, and 100=severe pain. Measurements of pain were made by the phlebotomist, a trained nurse observer and the patient. The observers and the patient were blinded as to whether active drug or placebo had been applied. Safety was assessed by visual observation of blanching or reddening at the site of application by the research nurse. The data were compared statistically using the Mann-Whitney U-test and variability expressed as ± 1 SD.

Results. The height and weight of the respective treatment groups were not significantly different. Forty eight patients received EMLA and 48 placebo, half were male and half female within each group. The duration of the EMLA application was 83 ± 34 minutes and the placebo 89 ± 28 minutes.

The mean pain measurements by the phlebotomist and research nurse were were 8 ± 13, and 7 ± 13 for EMLA, and 25 ± 28, and 32 ± 30 for placebo respectively. The mean pain measurements, by the patients, are illustrated in the Table.

Table. Mean Patient Pain Measurements

Age, yrs	EMLA	Placebo	p-value
5-6	17 ± 25 (12)	29 ± 39 (12)	0.4011
7-8	25 ± 26 (12)	42 ± 40 (13)	0.3398
9-10	7 ± 8 (12)	53 ± 33 (11)	0.0016
11-12	13 ± 17 (12)	68 ± 34 (12)	0.0004
Total	16 ± 21 (48)	48 ± 38 (48)	<0.0001

( ) = Number of patients studied

Four patients (8%) treated with EMLA had a cutaneous reaction at the site of application. Three of these were redness which lasted between 30 and 60 minutes, and one was blanching. One patient treated with placebo (2%) had redness at the site of application.

Conclusions. These studies, the only American investigation of EMLA, provide new data supporting the effectiveness and safety of the eutectic mixture of lidocaine and prilocaine for producing cutaneous anesthesia for venipuncture in children. Older children had better discrimination, probably related to a dimished fear of the sight of the needle.

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TITLE: MANNITOL VS. LIDOCAINE FOR ICP CONTROL FOLLOWING CRYOGENIC BRAIN INJURY IN RATS.

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INTRODUCTION: Lidocaine and mannitol are often administered to decrease intracranial pressure (ICP) in neurosurgical patients. Lidocaine reduces both cerebral metabolic rate and cerebral blood flow (CBF) and increases cerebrovascular resistance,[1] resulting in a decrease in ICP in response to a reduction in cerebral blood volume.[2] Mannitol, an osmotic diuretic, is thought to reduce ICP by extracting water from the cerebral extracellular space into the intravascular compartment. The relative efficacies of lidocaine and mannitol, however, are uncertain. We therefore compared the effects of these agents on ICP, CBF in Sprague-Dawley rats following a standardized cryogenic brain injury.

METHODS: With the approval of the local Animal Care Committee, 29 male Sprague-Dawley rats weighing 250-350 gm were anesthetized with 3%-3.5% halothane in 100% O_2, while cannulae were placed in the femoral artery and vein and trachea. Halothane was discontinued and anesthesia was maintained with alpha chloralose, 50 mg/kg, I.M., and d-tubocurarine, 0.5 mg/kg,IV. Ventilation was controlled with 100% O_2 to maintain normocarbia. The animals were placed on a stereotactic frame and 3 burr holes were made on the skull. 300µ platinum probes were placed in the right and left caudate nuclei for measurement of CBF using the inhaled hydrogen clearance technique.[3] A Camino pressure transducer was inserted into the right parietal epidural space for measurement of ICP. Mean arterial pressure (MAP), ICP, and temperature were monitored continuously. All skin and muscle edges were infiltrated with 0.05% bupivacaine. A cryogenic cerebral injury was created by direct application of liquid nitrogen for 25 sec through a cryoprobe placed over the skull above the right cerebral cortex. ICP increased by 9.1 mm Hg±0.8 SEM over pre-lesion values. When ICP remained constant at ±2 mm Hg for 30 min, post-lesion measurements were performed. The animals were then randomized to receive a 15 min intravenous infusion of either: 1) 0.9% saline placebo, 2) lidocaine, 5 mg/kg, or 3) mannitol, 1gm/kg. A fourth group of animals was fully monitored but received no cerebral lesion and no drug treatment. CBF and ICP were recorded at 10 min and 90 min after the treatment drug was given. At the end of the study, 3% Evan's blue dye, 1 ml, was given IV, and the brains were sliced to assure that the CBF probes were in proper position.

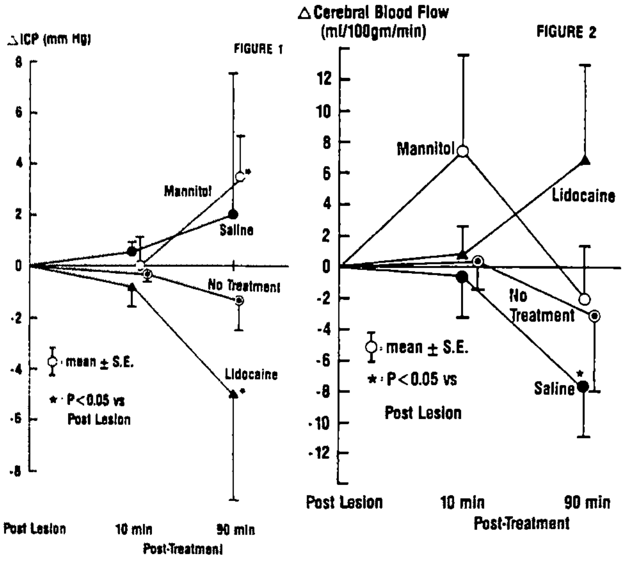
RESULTS: Throughout the study period the $PaCO_2$ and core temperatures were held constant at 38.6 mm Hg ±1.4 SE and 37.2°C ±0.2 SE, respectively. Figures 1 and 2 summarize the results of the changes in ICP and CBF. No change occurred in ICP, CBF or MAP in the animals with no cerebral lesion and no drug treatment. Lidocaine, however, produced a significant decrease in ICP 90 min after treatment, with no change in CBF or MAP. In contrast, mannitol produced a significant increase MAP 10 min after infusion which was accompanied by a tendency for CBF to increase. ICP was unchanged at 10 min but significantly increased 90 min after treatment. At this time there was no change in CBF or MAP from post-lesion values. After saline-placebo, there was a tendency toward an increase in ICP at 90 min after treatment and a significant decrease in both CBF and MAP.

DISCUSSION: This study demonstrates that in the presence of cerebral injury and decreased intracranial compliance, lidocaine was more effective than mannitol in reducing ICP and maintaining CBF. In contrast, mannitol was no better than saline-placebo in preventing increased ICP and decreased CBF. We conclude that I.V. lidocaine is superior to mannitol for control of increased ICP in this brain-injury model.

TABLE 1: Blood Pressure Changes During Study

Treatment:	Before	Post 10 min	Post 90 min
None	134±9	134±9	131±9
Lidocaine	137±10	136±10	146±12
Mannitol	138±7	144±6*	130±9
Saline Placebo	148±7	131±7*	105±7

All values: Mean ± SE, * = P<.05 vs Pre-treatment



FIGURES 1 & 2: Changes in ICP and CBF before and 10 and 90 min after receiving no treatment, lidocaine, mannitol or saline placebo. The no-treatment group also had no cerebral lesion.

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TITLE: MIXED VENOUS OXYGEN SATURATION CHANGES ASSOCIATED WITH TOURNIQUET DEFLATION UNDER EPIDURAL ANESTHESIA FOR TOTAL KNEE ARTHROPLASTY

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INTRODUCTION: Hemodynamic changes associated with tourniquet use have been investigated previously,[1,2] but cardiac output(CO) changes are unknown. Core body temperature falls following tourniquet deflation(TD), invalidating thermodilution measurements[3]. Since CO determines mixed venous oxygen saturation(SVO$_2$) (at constant oxygen consumption(VO$_2$), hemoglobin, etc.),we examined SVO$_2$ changes following TD.

METHODS: Following institutional approval, data were gathered prospectively on 28 tourniquet deflations in eight patients receiving lumbar epidural anesthesia with bupivicaine 0.75% for bilateral total knee arthroplasty. All patients received nasal O$_2$ and EKG, pulse oximetry, and radial artery monitoring on the contralateral upper extremity. An oximetric pulmonary artery catheter (Spectromed Model SP5547) was inserted via the right internal jugular vein. Catheters were calibrated in vitro prior to insertion according to manufacturer's specifications. In vivo calibrations were performed intraoperatively using a cooximeter(Corning 2500). Thermodilution CO was measured in triplicate prior to TD. SVO$_2$, mean arterial pressure(MAP), mean pulmonary artery pressure (MPAP) and core temperature(T°) were recorded immediately prior to TD(T$_0$), and each subsequent 10 seconds for 180 seconds. Results were analyzed using Student's t-Test or chi-square.

RESULTS: Continuous SVO$_2$ values correlated well with cooximetry measurements(r=0.77,bias=-0.2,precision=±4.0). Following TD, the mean SVO$_2$±SD fell from 76.0±5.4% to 58.5±8.5%. The time from TD to the nadir SVO$_2$ was 46±19 seconds. Neither the magnitude of the change in SVO$_2$ nor the time to reach the nadir correlated with tourniquet time, cardiac index prior to TD, or MAP and MPAP changes following TD. As a group, mean SVO$_2$ fell significantly by 10 seconds, reached nadir at 50 seconds, and then steadily rose but was still below baseline at 180 seconds.(Fig. 1) Fall in MAP followed a similar time course, but had not shown a tendency to return to baseline by 180 seconds.(Fig. 2) This fall in MAP was a 28.5±8.6% decrease from a baseline MAP of 82.8±11.9 mmHg.(Table 1) Also shown in Table 1 are the decreases in MPAP and T° associated with TD. No patients exhibited changes in arterial oxygen saturation(SaO$_2$) as measured by pulse oximetry.

DISCUSSION: This study confirms our previous findings that in this patient population, the hemodynamic changes that follow TD occur quickly and are profound.[1] Several factors may contribute to the acute decrease in SVO$_2$. Immediately following tourniquet deflation, the oxygen depleted blood in the lower extremity returns to the venous circulation, lowering the oxygen content of mixed venous blood. Oxygen debt in the previously ischemic limb may cause increased oxygen extraction from the blood(i.e. increased VO$_2$), resulting in a fall in SVO$_2$. In addition, a reduction in CO due to venous pooling in the previously ischemic lower extremity(decreased preload), or due to myocardial depression from circulating ischemic metabolites, might further decrease SVO$_2$. In spite of this fall in SVO$_2$, no patient demonstrated a change in SaO$_2$. However, patients with pulmonary shunting might have transient falls in SaO$_2$ following TD.

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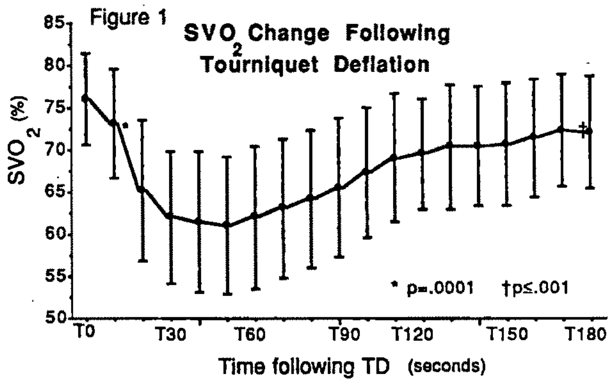
Figure 1 SVO$_2$ Change Following Tourniquet Deflation

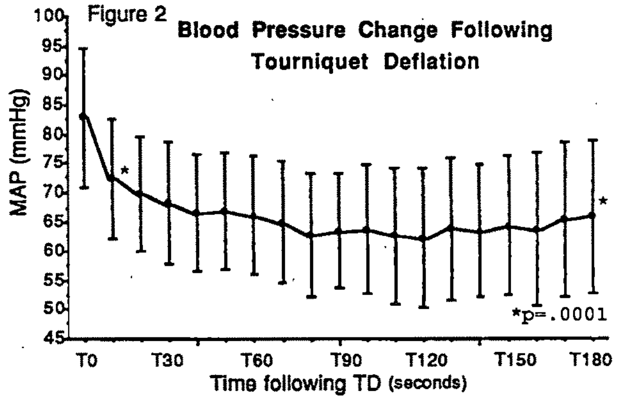
Figure 2 Blood Pressure Change Following Tourniquet Deflation

MAP, MPAP, and Temp Changes Following Tourniquet Deflation

TABLE 1

	T_o	Nadir	% Drop
MAP (mmHg)	82.8±11.9 (n=28)	58.9±9.6 (p=.0001)	28.5±8.6
MPAP (mmHg)	19.5±3.8 (n=22)	15.3±2.5 (p=.0001)	20.7±10.9
Temp (°C)	36.4±0.4 (n=9)	35.9±0.3 (p=.0001)	

Title: STREPTOMYCIN INHIBITS CHOLINE ACETYLTRANSFERASE ACTIVITY

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Introduction:

Antibiotics not only produce muscle paralysis at very high concentrations, but also potentiate the neuromuscular blockade induced by muscle relaxants at therapeutic concentrations (1-2). Investigators ascribed the mechanisms for the antibiotic-induced potentiation of neuromuscular blockade to either prejunctional and/or post junctional neuromuscular effector sites. Certain drugs are known to interfere with acetylcholine (ACh) synthesis by inhibiting choline acetyltransferase (CAT) activity. Such an inhibition caused by antibiotics could provide an additional mechanism for the antibiotic-muscle relaxant interaction. To our knowledge the effect of antibiotics on CAT activity has not been published. Therefore, we studied the effect of streptomycin on CAT activity.

Methods:

Choline acetyltransferase activity was determined by a radiochemical method modified from those of Schrier and Shuster, and Sastry and Henderson in which the labelled acetyl group is enzymatically transferred from [14c]ACOA to choline. The assay for CAT activity was developed as follows. The total volume of the mixture was 0.3 ml which was composed of three 0.1 ml aliquots added sequentially to a 75x10 mm test tube. The first 0.1 ml aliquot consisted of 0.1 ml of buffer-incubation mixture. The second aliquot of 0.1 ml buffer was reserved for dissolving various compounds, such as inhibitors, activators and additional substrates. The third aliquot of 0.1 ml consisted of the purified placental enzyme in NaCN EDTA solution. The effect of streptomycin in concentrations of 10^{-6} M and 10^{-3} M was studied on CAT activity using 6 different enzyme samples.

The basic principle of this assay is the conversion of [14c]ACOA to [14c]ACh by CAT in the presence of choline. A fixed variable substrate was dissolved in the first aliquot of buffer=incubation solution while the variable compound (substrate or inhibitor) was dissolved in the second aliquot of 0.1 ml of buffer. The reaction was started by the addition of the enzyme to 0.1 ml of the preincubated buffer solution (37°C) and incubated for 10 min. The reaction was stopped by pouring the contents of the tube on the column. 0.5 ml of distilled water was added to the empty incubation tube and poured over the column. Water was allowed to disappear from the top of packing and this procedure was repeated four more times at 5 min intervals. The effluent was collected in scintillation vials and 15 ml of aqueous counting scintillant was added. The CAT activity was measured as counts per min and expressed as unit.

Statistics: Two way ANOVA and Duncan's new multiple range test was used to analyze the data. A P value <0.05 is considered significant.

Results:

Results are shown in the table. The mean control CAT activity was 947±42 units. CAT activity reduced to 797±56 and 827±36 at streptomycin concentrations of 10^{-6} M and 10^{-3} M, respectively.

Table: Effect of Streptomycin on CAT Activity (units)

Streptomycin Concentration	CAT Activity Mean±SEM	% Inhibition of CAT Activity
Control (0)	947±42	-
10^{-6} M	797±56	16*
10^{-3} M	827±36	13*

* = P<0.05 (ANOVA)

Discussion:

A large number of antibiotics, both aminoglycoside and non-aminoglycoside groups, are known to have neuromuscular blocking properties. Pridgen reported the first clinical cases of antibiotic-induced neuromuscular block. The mechanisms by which antibiotics potentiate the neuromuscular blockade produced by muscle relaxants appears to be confusing. Investigators ascribed these mechanisms either to prejunctional and/or postjunctional neuromuscular effector sites. There is evidence to suggest that aminoglycosides, including streptomycin potentiate the action of muscle relaxants primarily by a calcium reversible prejunctional mechanism. Investigators also demonstrated that both aminoglycosides and non-aminoglycoside types of antibiotics possess postjunctional blocking properties.

Choline acetyltransferase (CAT) is the principal enzyme responsible for the synthesis of acetylcholine. CAT is a slowly acting enzyme when compared to catabolizing enzymes of ACh,namely acetylcholinesterase and pseudocholinesterase. However, there are storage mechanisms for ACh at the nerve terminal to meet the demands. In spite of the large reserves of acetylcholine at the nerve endings, tetanic fade can be elicited even in the absence of neuromuscular blockers if strong enough stimuli are applied to the nerve. A small decrease in the synthesis and/or release may significantly contribute to the action of nondepolarizing muscle relaxants. This is probably more important in patients with certain muscle disorders like myasthenia gravis where the ACh reserves are already limited when compared to normal patients.

In conclusion, our data demonstrated that streptomycin has a small but significant inhibitory effect on choline acetyl transferase activity. Our data suggest an additional mechanism for the streptomycin-induced potentiation of neuromuscular blockade from nondepolarizing muscle relaxants.

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Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University.

TITLE: INHIBITION OF PLASMA CHOLINESTERASE BY BETA ADRENORECEPTOR ANTAGONISTS

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Introduction. Propranolol is a potent inhibitor of plasma cholinesterase (1). Analysis of various beta adrenoreceptor antagonists revealed similarities in the chemical structure. Additionally, several beta adrenoreceptor antagonists are associated with profound refractory bradycardia after patients were given anticholinesterase drugs for the reversal of the neuromuscular blockade. The mechanism of the interaction between beta adrenoreceptor antagonists and anticholinesterase drugs is unknown. We studied the effect of Atenolol, Esmolol, Labetalol, Metoprolol, Pindolol, Propranolol and Timolol on plasma cholinesterase.

Methods. Plasma cholinesterase activity from a single healthy donor was studied by the Ellman method (2). Acetylthiocholine (ATCH) was used as the substrate of this enzyme. 10 ul of plasma was added to 100 ul of 10 mM 5, 5' dithiobis (2-nitrobenzoic acid) (DTNB), 1 ml of 1 mM ATCH and enough 0.1M potassium phosphate buffer, pH 7.5, to make the reaction mixture at a final volume of 3 ml. Enzyme catalyzed hydrolysis of ATCH produces thiocholine which reacted with DTNB to release a colored product,5-mercapto-2-nitrobenzoic acid, which was quantitated at 412 nm with a spectrophotometer to determine the enzyme activity. The reaction mixtures were routinely allowed to stand for one minute before kinetic analysis to eliminate possible overestimation of enzyme activity from the spontaneous hydrolysis of ACTH in stock solution. By including various amount of beta adrenoreceptor antagonists in the reaction mixture, the inhibition of cholinesterase was evaluated. All experiments were repeated three times and the average value were used. The 50 percent inhibition concentration (I-50) for each antagonists was calculated by probit analysis. Published plasma protein binding data (3,4) were used for the linear regression analysis.

Results. All beta adrenoreceptor antagonists inhibit plasma cholinesterase. I-50 for each antagonist was found to be as following: Propranolol, 1.0x10^{-6}M; Esmolol, 1.8x10^{-5}M; Pindolol, 1.9x10^{-5}M; Labetalol, 3.6x10^{-5}M; Metoprolol, 3.4x10^{-4}M; Atenolol, 4.1x10^{-4}M and Timolol, 4.8x10^{-4}M. A double reciprocal plot of the kinetic data with different substrate concentrations revealed that for Labetalol and Atenolol, the inhibition were noncompetitive in nature. The inhibition by all other compounds were competitive.

Discussion. The potency of various beta adrenoreceptor antagonists as plasma cholinesterase inhibitor depends on their protein binding in plasma (Fig). Propranolol, the drug with the highest protein binding fraction turn out to be the most potent cholinesterase inhibitor; whereas Atenolol, Timolol and Metoprolol, with low plasma protein binding fraction are much weaker cholinesterase inhibitors.

Esmolol, with steady state blood concentration of 1.6ug/ml (5.1x10^{-6}M) (3) produces a statistical significant prolongation of succinylcholine caused neuromuscular blockade (5). Labetalol, at therapeutic plasma concentration of 0.7-3 ug/ml (2-9x10^{-6}M) (3) could also cause clinically significant drug interaction. The therapeutic plasma level of Pindolol, Metoprolol, Atenolol and Timolol probably will be too low to cause significant plasma cholinesterase inhibition. The metabolites of each antagonist may also be inhibitors of cholinesterase and could cause drug interaction.

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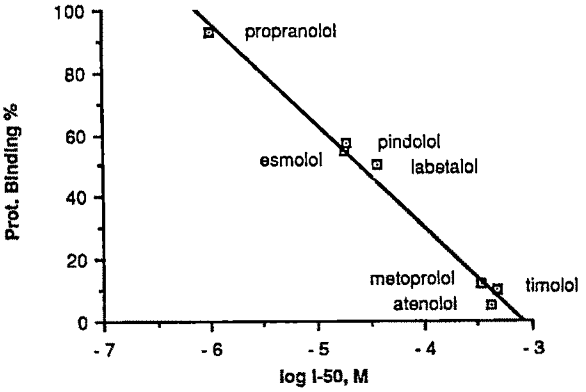

Fig: Semilogarithm plot of protein binding vs I-50 of various beta adrenoreceptor antagonists.

TITLE: INTRAMUSCULAR MIDAZOLAM FOR ANESTHESIA PRE-INDUCTION IN PEDIATRIC OUTPATIENTS

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An ideal pre-induction drug should be easy to administer, rapid acting, consistently effective even in an upset child and not result in prolonged sedation following short operations. The objective of this study is to examine whether midazolam is an effective pre-induction agent in unpremedicated children.

METHODS:

Institutional approval and parental consent were obtained to study 52 healthy children 18 mos - 4 yrs old scheduled for short surgical procedures (< 1 hr) as outpatients. No premedication was used. An inhaled mask induction was attempted on all patients, and their cooperation was objectively scored on a scale of 1 (very cooperative) to 5 (struggles and pushes the mask away).[1] Inhaled induction was continued in patients who scored 1-3 (n = 22). In children who scored 4 or 5 (n = 30), inhaled induction was stopped and midazolam 0.2 mg/kg IM was injected in deltoid muscle. Two minutes later, and every 60 sec. thereafter mask induction was again attempted and the response scored. The time from midazolam injection to mask acceptance was recorded. The cooperation score of children who refused mask induction initially was compared with their own score after treatment, using Wilcoxon test.

RESULTS:

Both groups were comparable in age. Duration of anesthesia and surgery, however, was significantly longer in the midazolam group. The median cooperation score in patients who accepted mask induction without sedation was 2. The cooperation score in patients who initially refused inhaled induction changed from a median of 5 to 2 within 5.0 ± 2.4 minutes following injection. Four patients (13.3%) continued to be upset 6 minutes or longer following administration of midazolam, and alternate induction techniques were employed. Although there was no significant difference in the recovery times among the two groups, the total hospital discharge time was significantly longer ($p < .01$) in patients who received midazolam than the control group (137 ± 55 vs. 60 ± 47 min, respectively).

DISCUSSION:

Most premedication studies compare the effects of different drug regimens or a placebo on a mixed group of children. It is often difficult to use the results of such studies to predict a similar effect when dealing with an individual child who is unusually apprehensive or disturbed and does ot cooperate with induction of anesthesia. Midazolam has been reported to be an effective premedicant agent when used in a dose of 0.08 mg/kg IM.[2] The results of the current study indicate that IM midazolam (0.2 mg/kg) is an effective pre-induction drug in children who do not cooperate with mask induction. Total hospital stay is prolonged, however. Further studiesmay be necessary to find if that prolonged effect may be eliminated by the use of benzodiazepine reversal agents such as flumazenil. The response to other pre-induction drugs e.g. IM ketamine or rectal methohexital should be evaluated in a similar fashion until the ideal drug or drug combination is discovered.

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Title: EFFECTS OF BUPIVACAINE AND LIDOCAINE ON CARDIAC FUNCTION IN AWAKE AND PENTOBARBITAL-ANESTHETIZED RATS

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Introduction. Evidence indicates that the neurotoxicity of bupivacaine is higher than that of lidocaine. However, the cardiotoxicity of bupivacaine versus that of lidocaine remains to be investigated. This study assesses the hemodynamic changes induced with subconvulsive doses of bupivacaine and lidocaine, with or without anesthesia.

Methods. The study was approved by the Baylor Animal Protocol Review Committee. Eight male rats (270-300 g) were instrumented under halothane anesthesia with a catheter in the abdominal aorta, a Doppler probe around the thoracic aorta, a wall thickness probe on the surface of the left ventricle, and a catheter in the internal jugular for drug administration. At least 7 days after surgery, animals received lidocaine (2.0 mg/kg low [L]; and 8.0 mg/kg IV, high [H]), and bupivacaine (0.5 mg/kg L and 2.0 mg/kg IV H). Each local anesthetic was administered awake and during pentobarbital anesthesia (30 mg/kg IV) on two separate occasions. Hemodynamic variables including mean arterial blood pressure (MAP), heart rate (HR), cardiac output (CO), thickening fraction (TF), stroke volume (SV), and systemic vascular resistance (SVR) were recorded before and after local anesthetic injections. Theoretical and animal experimental validations have established the measurement of ventricular thickening fraction as an index of regional myocardial contractility[1]. Data were analyzed using an analysis of variance followed by the Neuman-Keuls test when appropriate. Alpha was set at a level of 0.05.

Results. Hemodynamic properties of lidocaine and bupivacaine in awake and in pentobarbital-anesthetized rats are presented in table 1. In awake rats, bupivacaine induced a dose-dependent vasoconstriction associated with bradycardia and a decrease in CO and TF at the highest dose. During anesthesia, the vasoconstriction was attenuated. However, a decreases in HR, CO, and TF were recorded at both the high and low dose. In awake rats, lidocaine induced hemodynamic changes similar to those recorded with bupivacaine. In contrast, during anesthesia lidocaine induced a dose-dependent hypotension, bradycardia, and a decrease in CO. In addition, at the highest dose lidocaine also decreased TF. Finally, one rat died after a lidocaine study; convulsions occurred in three rats after lidocaine, and in one rat with bupivacaine.

Discussion. These data indicate that at equianalgesic doses bupivacaine and lidocaine produce similar hemodynamic changes in chronically instrumented rats. However, this study provides evidence that lidocaine is more cardiodepressant than bupivacaine when administered during pentobarbital anesthesia.

TABLE 1: Hemodynamic properties of bupivacaine and lidocaine in awake and pentobarbital-anesthetized (Pento) rats.

	MAP mmHg	HR beats/min	CO ml/min	TF %
Awake	107±10	358±22	69±11	23±2
Bupivacaine				
L	116±12*	345±21	64±14	20±11
H	143±15*	323±15*	53±11	17±9
Lidocaine				
L	114±7	351±25	69±12	20±8
H	128±14*	281±34*	36±15*	15±10*
Pento	80±13	343±21	67±12	19±11
Bupivacaine				
L	81±13	303±11*	59±12*	16±11*
H	90±10	256±26*	50±11*	16±11*
Lidocaine				
L	71±7	302±18*	59±13*	19±10
H	64±6*	247±29	46±9*	14±8*

Mean ± SD; *P < 0.05

Reference

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Title: DOES IT TAKE LONGER TIME TO INDUCE CHILDREN IN THE PEDIATRIC INDUCTION ROOM IN THE PARENT'S PRESENCE?

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INTRODUCTION:

Previous study has demonstrated that the parents' presence during induction of anesthesia in children appears to benefit the parents and the anesthesiologist, and thus also the child[1]. In order to do that, our institutional policy allows us to induce general anesthesia in children in the parents' presence, in a separate pediatric induction room, and then transport the anesthetized child to the operating room. Recently, the question has been asked:

"Does it take longer time to induce the child in the induction room in the parents' presence and then transport the anesthetized child to the OR than anesthetizing the child straight in the OR without the parents' presence?"

Thus, we undertook the following study to answer the above question and determine if there is any significant difference.

METHODS:

Following IRB guidelines, informed parental consent was obtained for 100 (Age 3 months - 12 years) ASA PS I or II children undergoing inguinal hernia, orchiopexy, BMT, or eye muscle surgery on an ambulatory basis. Children were randomly assigned to one of the two groups. General anesthesia was induced via a mask in all children using O_2/N_2O/Halothane. Group 1 children received anesthesia in the pediatric induction room across the hall from the main operating rooms. The child sat in the parent's lap and following induction of anesthesia, was put on a stretcher modified to transport safely the anesthetized child. Intravenous line placement, endotracheal intubation, and caudal block were performed in the induction room, if necessary for the surgery, prior to the transport to the OR. After transporting the child to the OR, the child was placed on the OR table and rehooked to the OR monitors and the anesthesia circuit. This completed the anesthesia induction. Time in minutes was noted using a stop clock from the time child entered the induction room to the time anesthesia induction was complete. Group 2 children were induced with general anesthesia straight on the OR table. Parents were not present. Time was again noted from the moment the child entered the OR to the time anesthesia induction was complete and the patient was ready for surgery. This time also included, like in group 1, time to perform procedures like intravenous line placement, intubation, and caudal block if deemed necessary for surgery. All patients were done by the same anesthesiologist and CRNA.

Data collected were analyzed for mean and SD and Student's T-test was done for statistical significance.

RESULTS:

Results obtained are given in the table. Childen who went through the induction room (Group 1) took 2.1 minutes longer for their induction to be completed than the children (Group 2) who went straight into the OR without their parents present (8.97 minutes). These differences are statistically significant.

	Group 1 (n=50)	Group 2 (n=50)
Age (yrs)*	3.9 ± 2.03	3.5 ± 3.6 **
No. of Procedures (Intubation, Caudal)	32	36
Anesthesia Induction Time (mins)*	11.0 ± 2.96	8.9 ± 3.70***

* (± SD) ** (NS) ***(P<0.005)

DISCUSSION:

The results of this study demonstrate a longer anesthesia induction time for Group 1 children. The longer time required in Group 1 is due to the transportation of the child from the pediatric induction room to the OR and to the reconnecting of the OR monitors and anesthesia circuits. In the author's opinion, the extra time taken to induce the child in the pediatric induction roon with the parents present is worth it especially when it benefits parents and the child[1].

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TITLE: EVALUATION OF INTRAVENOUS ESMOLOL FOR TREATMENT OF POSTOPERATIVE HYPERTENSION

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INTRODUCTION: Emergence from anesthesia elicits an adrenergic response which may precipitate transient but intense increases in blood pressure. Multiple factors have been hypothesized; these include arousal from anesthesia, withdrawal of antihypertensive medication prior to surgery, full bladder, pain at site of operation, and changes in renin-angiotensin system. Sometimes, this hyperdynamic state persists despite analgesia, infiltration of wound with local anesthetics, and removal of the stimulus of the endotracheal tube. The development of postoperative hypertension requires immediate assessment and treatment to reduce risks of myocardial infarction, arrythmia, congestive heart failure, bleeding and stroke.(1)

Esmolol is an ultra short acting parenteral beta adrenergic antagonist with rapid onset which has been successfully used intraoperatively to treat hypertension and tachycardia.(2-3) The objective of this study was to evaluate the clinical efficacy of esmolol, for treatment of hypertension following anesthesia in the recovery room.

METHODS: After IRB approval, informed consent was obtained from ASA physical status I-III patients (age 21-70 years). Subjects unsuitable for beta blocker therapy were excluded from the study. Study patients (n=30) underwent non-cardiac surgery under routine general anesthesia. If, on emergence from anesthesia in the operating room or in the recovery room, the patient developed systolic blood pressure (SBP) of ≥ 150 mmHg and/or diastolic blood pressure (DBP) ≥ 95 mmHg with a heart rate (HR) ≥ 70 bpm for at least 5 min in the absence of major acute pain, hypovolemia, anemia or hyperpyrexia, esmolol was administered as a continuous infusion. To initiate treatment, esmolol was administered as a loading dosage infusion of 40 mg/min for 1 min followed by a 4 min maintenance infusion of 4 mg/min. If an adequate therapeutic effect was not observed within 5 min, the same loading dosage was repeated, followed with a maintenance infusion increased to 8 mg/min.

Titration procedure as above was continued (i.e., loading infusion of 40 mg/min for 1 minute), increasing maintenance infusion by increments of 4 mg/min (for 4 min.) for a total of six steps. As the desired BP or safety endpoint was approached, loading infusion was omitted and incremental dose in the maintenance infusion was reduced from 4 mg/min to 2 mg/min or lower. **Efficacy endpoints were:** A decrease in SBP or DBP of at least 10% from the baseline measurement. **Safety endpoints were:** 1) a decrease in SBP < 100 mmHg or > 25% ; 2) HR < 60 bpm; and 3) maximum esmolol infusion rate of 24 mg/min. HR, SBP, and DBP were measured and recorded every 1-5 min using a DINAMAP. After selection of a proper dose level by titration, that infusion was maintained for 60 min. During this period, adjustment of the infusion rate was made to maintain SBP in the 100-140 mmHg range. After 60 min, when esmolol infusion was discontinued, patients entered a follow-up period. Prior to esmolol administration (baseline), and at end of titration changes in SBP, DBP and HR were analyzed statistically using ANOVA. Therapeutic success, failures, and adverse experiences were also noted.

RESULTS: 30 patients (mean age (yrs) 53.2 ± 13.1; 20 females and 10 males; mean weight (kg) 80.8 ± 23.6) were entered into the esmolol study. As shown in Table 1, there was significant difference between beginning (baseline) and end of esmolol titration SBP, DBP, and HR. These patients received anywhere from 100 mg to 2104 mg of esmolol. Mean duration of the esmolol infusion was 63.6 ± 28.3 min. 10 patients received 1 step of esmolol titration (i.e., loading dose of 40 mg/min for 1 min followed by maintenance infusion of 4 mg/min for 4 min) to reach the endpoint. 11 patients received 2 titration steps, and 3 patients received 3 titration steps. 4, 5, and 6 titration steps were received by 2 patients each to reach the endpoint. Other results are given in Table 2.

TABLE 1.

	BASELINE	END OF TITRATION withESMOLOL
SBP	164.2 ± 15.2	128.9 ± 16.9*
DBP	95.8 ± 10.1	74.5 ± 14.0*
HR	91.3 ± 15.1	69.2 ± 10.6*

* $p < 10^{-6}$

TABLE 2.

ADVERSE EFFECT:	
Bradycardia < 55 bpm	n = 4
Respiratory Stridor	n = 1
THERAPEUTIC EFFICACY:	n = 27 (90%)
SAFETY ENDPOINT REACHED:	n = 10 (33%)

DISCUSSION: Esmolol is a beta adrenergic blocking agent with rapid onset and short elimination half-life (9 min). Esmolol decreases the BP by primarily inhibiting the beta one receptors located mainly in the cardiac muscle; however at high doses beta one selectivity is lost and esmolol begins to inhibit beta two receptors located primarily in bronchial and vascular musculature. With efficacy as high as 90% and fewer side effects, esmolol joins the armamentarium of other drugs for the treatment of postoperative hypertension.

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TITLE : COMPARISON OF THE EFFECTS OF PROPOFOL AND THIOPENTAL ON MYOCARDIAL CONTRACTILITY AND ISCHEMIA, USING THE ISOLATED PERFUSED RAT HEART.

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INTRODUCTION Induction of anaesthesia is frequently associated with hypotension and a reduction in cardiac output. Thiopental may be associated with hypotension due to a direct negative ionotropic effect, and hypotension following propofol administration may be associated with reduced systemic vascular resistance or decreased left ventricular filling pressures[1]. However there are no published data to date concerning the effects of propofol on contractility in isolated heart preparations, and little is known about the comparative effects of propofol or thiopental on the leakage of intracellular proteins or ions during myocardial ischemia. Magnesium and Potassium leakage may contribute to dysrhythmia development during myocardial ischemia[2]. The objectives of this study were to compare the effects of propofol and thiopental on cardiac contractility and, on the leakage of myocardial protein and ions following myocardial ischemia.

METHODS Following instituitional Ethics Committee approval, 27 rats were randomly allocated to 3 treatment groups : group 1 (n=9) control, group 2 (n=9) propofol and group 3 (n=9) thiopental. A standardised protocol of intraperitoneal heparin (500 IU), ether anaesthesia and cervical dislocation was followed in all cases. The hearts were rapidly excised and perfused in the Langendorff mode[2], with oxygenated Krebs' buffer (95% 0_2, 5%$C0_2$, pH: 7.4, T: 37 °C). Contractility during the initial 5 mins (baseline contractility) was measured using a Washington recorder. The perfusate was then changed to identical buffer containing no anaesthetic (controls), propofol (1.6μg/ml), or thiopental (58μg/ml). The concentration of thiopental was determined by product of (relative potency) x (free fraction ratio). Contractility was recorded for the following 30 mins (experimental phase). All preparations were electronically paced. The effluent perfusate was then sampled (500μl), and global ischemia was applied by discontinuing the perfusate for 60 mins whilst maintaining normothermia. The hearts were then reperfused and the initial 500μl effluent was retained. All samples were assayed for Mg, K and total protein concentration. Data was expressed as mean ± SEM. Statistical analyses included paired and unpaired Student's t-test, $p < 0.01$ was considered significant.

RESULTS The contractility scores (ratio of experimental to baseline contractility), is illustrated in Fig.1. Thiopental was associated with reduced contractility compared with controls. Propofol was not associated with reduced contractility. The concentrations of protein, K and Mg were all greater in the post- compared with the pre-ischemic effluent perfusate samples. The magitude of the Mg elevations is illustrated Fig. 2. A significantly greater leakage of Mg was observed in the thiopental group than in the propofol or control groups. However the magnitude of the K and protein leakage was not significantly different in any of the groups.

DISCUSSION In this study propofol was not associated with a negative ionotropic effect, unlike an equipotent free concentration of thiopental. The negative ionotropism induced by thiopental did not protect against myocardial cell damage in that there was no reduction in protein or ion leakage in this group[3]. Protein leakage is thought to accurately reflect the extent of myocardial ischemic damage[2]. The thiopental group showed a greater Mg efflux but not protein or K leakage compared with the propofol and control groups. This may suggest a selective effect of thiopental on myocardial Mg loss during ischemia, which could have important implications for development of dysrhythmias[2].

Fig.1

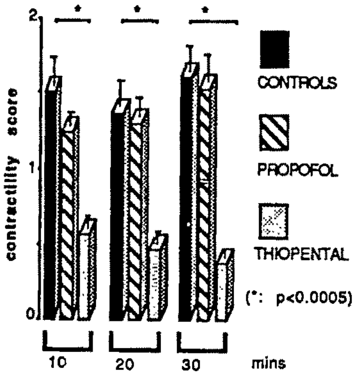
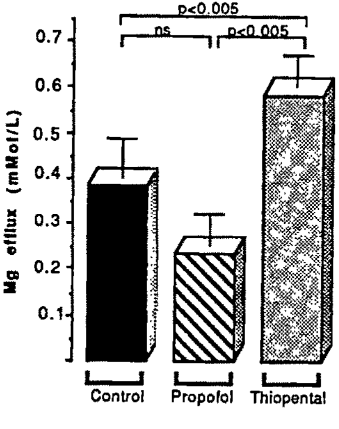


Fig.2



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Title: **OVER FIFTY PERCENT OF DISPOSABLE CIRCUITS LEAK**

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Introduction:

Disposable circuits have become so prevalent that it is hard to purchase the old black rubber elephant tubes. Four years ago, our hospital accountants convinced us that these plastic disposables were less expensive than the resources needed to clean and wash the nondisposable tubes. But with more than twelve manufacturers selling disposable circuits, how should we choose among them? Price or configuration of attachments and swivel connectors are the two usual determinants, a salesman told us. His assertion, "Other brands leak; ours doesn't," led us to test the hypothesis that there is a difference in the incidence of leaks on different circuits.

Methods

Through trades with other institutions and suppliers, we received at least 6 "stock" circuits of 12 different disposable circuits and 2 different nondisposable circuits. Among the disposable circuits of different styles were 2 from Dryden, 3 from King, 2 from Marquest, 2 from Kendall, 1 from Intertech Ohio, 1 from Vital Signs, and 1 from Baxter. We tested all circuits individually for leaks on three different anesthetic machines. The bag of each was placed where the endotracheal tube would be connected, and mechanical ventilation with a peak pressure of 30 mmHg was used to drive into a circuit a gas mixture of 5% isoflurane in 5 L/min O_2. After 30 seconds for equilibration, a halogen sniffer (TIF instruments) was used to check for leaks at each junction point (3-7 per circuit), at all swivel points (0-2 per circuit), and along the tubes. We attempted to reseal the junctions of any leak detected, and then retested for leaks with a halogen sniffer, mass spectrometry, and infrared detection devices. Circuits were tested in random order, and the test recorders were blinded to circuit manufacturer. A leak was considered significant if over 0.1% isoflurane could be detected 5 mm or more from the circuit. Statistical analysis included Fisher's exact test with Bonferonni correction.

Results

The results appear in the table below.

	number leaking number tested	number with significant leak number tested
Disposable Brand		
1	7/8*	5/8**
2	5/6*	2/6
3	3/10	0/10
4	3/6	3/6
5	3/11	1/11
6	5/6*	2/6
7	7/10*	3/10
8	9/10*	4/10
9	2/6	2/6
10	2/6	0/6
11	5/6*	5/6**
12	6/6*	6/6**
Old Rubber		
1	0/6	0/6
2	0/6	0/6

* significant difference from old rubber at $p \leq 0.05$
** significant difference from old rubber at $p \leq 0.05$

Discussion

Although the disposable circuits of all manufacturers had readily detectable leaks in at least 25% of their circuits, are these leaks a significant source of contamination in the OR? At the conditions tested (peak pressure of 30 mmHg) leaks generating a concentration of 1/50 or more of inspired concentration of gases would have occurred in more than 33% of all tested circuits, exceeding acceptable NIOSH levels 5 mm away from the circuit, and those deemed acceptable by the occupational safety committee of the A.S.A. We could, however, find no firm data to support this degree of contamination as dangerous. The old rubber tubes also leak to this degree if their junctions are not correctly seated. Of the 6 tested, only one machine at our institution produced leaks in any other area, including other areas of the absorber circuit. Cost of disposable circuit did not correlate with degree of leak, as the best circuits (#3,5,10) were from the relatively high-priced (Intertech Ohio) and the low-priced (King systems) suppliers, and the leakiest circuits (#1,8,11,12) were from both high- and low-priced suppliers (Dryden, Baxter, and King). More swivels and junctions tended to correlate, but not absolutely, with greater contamination propensity.

Thus, perhaps another price, in addition to space utilization and plastic disposal pollution, must be added to the use of disposable circuits, that of operating room environmental contamination.

Title: *EFFECT OF PREOPERATIVE INTRAMUSCULAR RANITIDINE ON GASTRIC ACIDITY AND VOLUME IN CHILDREN*

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Introduction. *The H -receptor antagonists are recent additions to the preanesthetic prophylaxis of the acid aspiration syndrome associated with anesthesia (1-3). Ranitidine is a relatively new, potent, highly selective H -receptor antagonist with minimal side effects (2,3). It was reported that suppresion of gastric secretion by ranitidine continues for more than 12 hours in adults (3). However, there is no report on preoperative administration of ranitidine in children. Therefore, we evaluated effects of preoperative intramuscular administration of ranitidine in pediatric patients.*

Methods. *Fifty four children with a mean age of 5.4 ± 1.0 years who sheduled for elective surgery under general anesthesia were studied after institutional approval and informed consent from parents. Patients were randomly divided into 3 groups, and all patients received bromazepam suppository 3 mg 2 hour prior to induction of anesthesia. Patients in group A received no ranitidine, while patients in group B received ranitidine 1 mg/kg and those in group C 2mg/kg i.m. 2 hour prior to induction of anesthesia.*

Following induction of anesthesia and tracheal intubation a gastric tube (10 or 12 Fr.) was passed and gastric contents were collected and analyzed for pH and volume, which was repeated every hour till the end of the operation. Plasma ranitidine levels were also measured at the time of induction of anesthesia by high performance liquid chromatography.

Results. *Mean values of age and body weight(kg) were 6.5 ± 1.0 and 22.2 ± 2.5 for group A, 4.7 ± 0.9 and 19.1 ± 2.5 for group B, and 5.3 ± 0.8 and 20.0 ± 2.0 for group C, respectively. There was no significant difference in age and body weight between groups. Gastric pH immediately after induction of anesthesia revealed 2.2 ± 0.3 for group A, 4.6 ± 0.7 for group B, and 6.7 ± 0.2 for group C, respectively. Values of pH in groups B and C were significantly higher than that of group A. These pH was maintained till 3 hour following induction of anesthesia (Fig.). Gastric volume immediately after induction of anesthesia revealed 21 ml for group A, 2.4 ml for group B, and 3.2 ml for group C. Values of groups B and C were significantly less than that of group A. Gastric volume decreased in each group gradually, but it was less in groups B and C during the study. The plasma ranitidine levels revealed 228 ± 32 ng/ml in group B and 487 ± 59 ng/ml in group C. No major adverse side effects attributable to intramuscular ranitidine were observed.*

Discussion. *Our results confirmed that preoperative administration of ranitidine in children caused significant reductions of both acidity and volume of gastric contents during anesthesia. Regargitation with subsequent pulmonary aspiration of gastric contents is a recognized hazard in anesthesia. Silent regurgitation of gastric contents may easily occur in pediatric patients since cuffless endotracheal tubes are utilized. It was generally agreed that a gastric pH lower than 2.5 and a gastric volume of 0.4 ml/kg tend to produce severe pulmonary damage. In our data the proportions of patients who had a gastric pH lower than 2.5 and a volume of less than 0.4 ml/kg immediately after induction of anesthesia were 71% in group A, 13% in group B and 0% in group C. It will be recommended that ranitidine 2 mg/kg is employed to prevent acid aspiration syndrome more accurately.*

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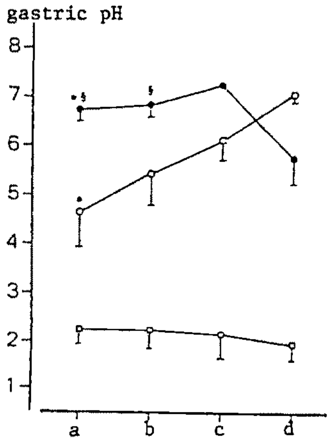

Fig. Changes in pH of gastric contents in groups during anesthesia. Squares for group A, open circles for B, closed circles for C.
* $p < 0.05$ vs group A
§ $p < 0.05$ vs group C

a: immediately after induction
b: 1 hr after induction
c: 2 hr after induction
d: 3 hr after induction
mean ± SEM are shown

TITLE: HEMODILUTION, REGIONAL BLOCK AND CESAREAN SECTION

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INTRODUCTION: Recently, infusion volumes of 1.5-2 L of crystalloid prior to spinal or epidural block before cesarean section (C/S) have become routine. This study quantitates the degree of hemodilution and augmentation of circulating blood volume (CBV) resulting from this infusion regimen. Results in hypo- vs normotensive patients are separately described.

METHODS: Human investigation committee approval and informed consent were obtained. Twenty normotensive ASA class 1-2 patients presenting for elective C/S under epidural (N=13) or spinal (N=7) anesthesia were evaluated. A minimum volume of 1 L of lactated Ringer's solution was given at the rate of 80-120 ml/min via rapid gravity infusion before attempting blocks and similarly infused until abdominal incision occurred. Patients received 1.5-2 L of infusate before the first injection of local anesthetic. A definition of hypotension at 90 systolic and a mean of 65 mm Hg was chosen as a safe lower limit of blood pressure for these normotensive parturients and yet clearly represent hypotension. One ml of blood was withdrawn and hematocrit (HCT) determined before fluids were infused and again just before surgical incision. Left uterine displacement occurred with supine positioning. Changes in CBV were calculated via HCT changes as follows:

$[HCT_{st}/HCT_{end} X\ 100]-100 = \%\ Incr\ in\ CBV_{st}$

RESULTS: The incidence of hypotension, extent of block, mean infused volumes (2.6 ± 0.5 L) and changes in CBV and HCT were similar in patients receiving epidural and spinal block. Preinfusion HCTs ranged from 31-44.5% (mean=38.3±3%). Post infusion HCTs ranged from 28-36% (mean= 31.6±2.4%). After infusions alone, 75% and 30% of the patients were anemic (HCT<34%) and markedly anemic (28-29% HCT), respectively, although only one parturient was anemic prior to anesthesia. The maximal drop in HCT was 12.5%. Hypotension occurred in 35% of patients, but was absent in those patients developing a decline in HCT<6% or an increase in CBV<15% (P=0.05; T-test). The mean increase in CBV was 21.6 ± 8.5% over baseline.

DISCUSSION: The lack of hypotension in the patients developing minimal declines in HCT and increases in CBV was an interesting and unexpected finding, as hypotension is commonly ascribed to inadequate augmentation of CBV. Intravenous fluid preloading with 1.5-2 L fixed volumes prior to initiating regional block represents only one approach in preventing hypotension. Routine preload volumes greater than 2 liters are not advocated or appear warranted, as hypotension was frequently encountered, will not reliably be eliminated with infusions alone and was well tolerated when treated immediately. Indiscriminant use of large preload volumes in all patients may lead to complications of hypervolemia in some, as fasted parturients in earlier studies were noted to develop acute hypervolemia at delivery (CVP measurements above norm) after one or two liter preloading therapies.[1,2] The high rate of ischemic ECG changes (55.7%) noted during C/S under regional anesthesia may be associated with hypervolemia and increased cardiac output at term, while venous air embolism seems less likely.[3,4] Up to delivery, a well tolerated hypervolemia may help sustain normotension, but lead to symptoms when constriction of the empty uterus leads to a physiological reduction in intravascular capacity, increased blood return in the absence of vena cava compression and a rise in central venous pressure. Patients presenting for C/S after a trial of labor are routinely hydrated throughout labor and may present with an augmented intravascular volume, a limited reduction in HCT with infusion and a reduced ability to tolerate excessive intravenous fluid loads, as they frequently receive oxytocic drugs exhibiting antidiuretic actions.

A large prospective study focusing on maternal and fetal outcome/side-effects is needed to define the optimal standard prehydration regimens. This study should incorporate prompt vasopressor support of blood pressure, rather than use vasopressor administration to indicate an inadequacy of the technique. While infusion of appropriate volumes remains the cornerstone in preventing hypotension, vigilance and prompt vasopressor treatment of hypotension will remain the hallmark of optimal obstetric anesthetic care and is not associated with adverse fetal outcomes. Knowledge of the preoperative reduction in HCT may be of particular value in determining the need for subsequent red cell transfusions, particularly as physicians utilizing the "Hbg 10 gm% / Hct 30%" rule as a transfusion trigger are still encountered. This level is excessive for most post-partum patients and is frequently above post-infusion levels.[5]

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TITLE: CONTAMINATION OF DRUGS IN AMPULES - CONTAINER AS CULPRIT!

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INTRODUCTION:Glass particle contamination of drugs marketed in glass ampules is ubiquitous during ampule opening and has been previously described, as well as consequences, hazards and possible methods of prevention$^{1-4}$. Previous studies have concentrated only on the glass itself as a contaminant. This is the first clinical study which examines the incidence of drug contamination with particles from the external ampule surface liberated upon opening.

METHODS: The external 5-6 mm wide ampule neck surface of 15 10ml ampules (Astra Xylocaine 2%) were painted with 3 coats of a saturated methylene blue (MB) solution and allowed to dry. This resulted in a dense, adhesive coat of MB. Fifteen untreated ampules of the same type served as controls. Nurse anesthetists and Anesthesia residents were asked to first open an untreated and then a MB treated ampule and draw the content through a 21G needle into a 10cc syringe. This occurred under typical clinical conditions as per the individual's routine. We recorded during opening the use of protective (against laceration), desinfecting or contaminating measures, breakage characteristics of ampules (regular=no free fragments noted and < 2 mm variation of jagged edge height on ampule neck) and noticeable MB contamination of needle and hub. Spectrophotometric measurement of absorption at 660 nm of all samples occurred serially while alternating control vs MB samples, to exclude systematic errors. The absorption and rates of contamination in the two groups were compared using Chi^2- with Yate's correction and 1-tailed t-test. We considered contamination to be significant when P<0.05 and to be evident when absorption values exceeded mean + 3 standard deviation (SD) of control values.

RESULTS: Mean absorption X 10^{-3} (± SD X 10^{-3}) of untreated, MB treated and contaminated ampules was found to be 0.3±0.5, 5.3±6.7 and 9.6±6.6 respectively. The difference in absorption in untreated vs MB treated groups was highly significant (P=0.006, t-test). Absorption values >1.8 X 10^{-3} indicated contamination from the external ampule surface. Eight ampules in the MB-treated group met this criteria and the contamination was significant (P=0.039, Chi^2-test). In 2 cases, no contamination was apparent via photometer analysis despite the fact that clinically, MB contamination of the needle exterior surface, hub and interior surface of the needle cap was clearly evident as blue coloured drops. Clearly 66% of the syringes were clinically contaminated (P=0.0005, Chi^2-test). Five MB-treated ampules broke in a highly irregular fashion and in 4 of these, the extent of surface glass fragmentation exceeded the width of the MB coated area. In 2 of these 4 cases, no photometric contamination was evident, although one of the 2 had MB contamination of the needle and cap, as stated above. Large, full-thickness or superficial fragments (as large as 2.5 mm diameter) were noted to be liberated from the ampule necks outside of the MB treated area. Only 27% of our personnel used alcohol desinfection prior to snapping open the ampule, while non-sterile procedures, including gauze or coattails to protect against laceration (20%) or no protection (53%) at all, were most commonly used.

DISCUSSION: Identifiable contamination of the ampule content with the external ampule surface material was demonstrated in 66% of all samples. We expected to detect an even higher incidence, as glass fragment contamination of 10ml ampules has been shown to approach 100%^{2}. Our methods may not have been sufficiently sensitive to detect all contamination from the external surface, as fragments were liberated from MB-unpainted surfaces and contaminated drug was immediately drawn up through small bore needles. The large volume (10 cc) of solution may, by dilution, have limited detection to only substantially contaminated ampules. Often ampules are carried in pockets (narcotics in anesthetic practice), intimately handled, stored on dusty shelves and not generally desinfected before opening, so that any contamination of the drug with particles originating form the ampule surface will be associated with microbial contamination. The high contamination rate found here with ampule use is significant statistically and clinically. Routine external desinfection of ampules before opening is recommended, particularly when treating immunosuppressed patients or when administering drugs via central intravenous lines. Improved container designs (i.e. Luer-lock openings) appear desirable to minimize nosocomial infections of patients, to eliminate sharp edges and needle use during drug administration into IV lines and to minimize injuries to personnel.

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TITLE:NEURAXIAL MORPHINE PLUS INTRAVENOUS PATIENT CONTROLLED ANALGESIA-NEW METHOD IN POSTCESAREAN ANALGESIA.

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INTRODUCTION:Neuraxial morphine (NM) administration combined with patient controlled analgesia (PCA) has not been previously described but has been routinely used in our institution for 4 years without incident. The effects of NM administration on postoperative PCA meperidine utilization was retrospectively studied in post cesarean section (CS) patients.

METHODS:Patients receiving PCA (Abbott Lifecare PCA Infusor) after CS as of Jan.1,1989, were studied via chart review and this study did not require Human Investigation Committee approval. To date, 36 charts were reviewed. All parturients underwent CS utilizing spinal or epidural anesthesia. All patients received intravenous (IV) PCA meperidine (10 mg/ml for each PCA dose, with a lockout interval of 6 minutes). In addition to PCA, group 1 (n=15) received intraoperatively either 3.0 (epidural) or 0.25 mg (spinal) of morphine as per clinical routine for each regional technique. PCA was initiated with the patient's first demand for pain medication and the cumulative amount of meperidine is routinely charted at 4 hour intervals. We evaluated the effects of NM during the first 24 hours post partum upon the time between delivery and first PCA dose as well as the cumulative and non-cumulative amount of PCA used during each 4 hour interval. Statistical significance was assumed when $P<0.05$.

RESULTS: Patients receiving neuraxial morphine demonstrated a longer pain free period until requiring the first postoperative analgetic dose 4.5±3.4 (mean hrs ± SD) than those receiving PCA-only 2.8±1.3, although statistical significance was not noted ($P=0.077$). The morphine group used statistically less cumulative meperidine at all times (Fig. #1). Meperidine usage after NM was markedly reduced during each 4 hour interval for up to 20 hours post delivery over the group receiving PCA-only. Cumulative 24 hr PCA meperidine usage in patients receiving NM was slightly less after intratheal (200 ± 221mg) than epidural (340 ± 263mg) administration but was, as well as the 4 hour interval requirement, very similar statistically. Cumulative PCA usage ranged from 50-730mg and 230-1270mg in the NM vs PCA-only groups, respectively.

DISCUSSION:Narcotic drugs are very closely and rigorously controlled by the pharmacy in our institution. This results in a very accurate accountability of PCA meperidine use at 4 hour intervals in our institution. While PCA analgesia affords greatest patient satisfaction, neuraxial morphine is associated with maximal analgesia.(1) We routinely utilize NM in minimal effective doses after CS to minimize undesirable side effects, while allowing patients to titrate residual analgetic needs via PCA. The logic of this approach is similar to that of PCA in addition to a baseline continual analgetic infusion. Our routine use of low doses of neuraxial morphine clinically reduces post operative CS pain and is substantiated by the significant reduction in PCA drug requirements documented here for up to 20 hours post delivery.

When inadequate pain relief is encountered after the administration of neuraxial morphine, many physicians anxiously administer fixed bolus doses of parenteral narcotics. We documented a very wide variation in analgetic requirements in both groups of patients. Fixed-dose parenteral bolus supplementation of NM analgesia will likely contribute to inadequate or overdosing of many patients, as well as lead to undesirable peak and trough effects with each supplemental dose. While higher doses of neuraxial morphine may reduce the need for additional analgetics, it may also increase the likelihood of side effects from the NM and parenterally administered supplemental analgetics.

This combination of neuraxial morphine with PCA has been safely utilized at this institution on the routine post surgical wards and may represent an ideal method to deliver superlative post operative analgesia. Further research into the safety and cost-effectiveness is warranted and planned.

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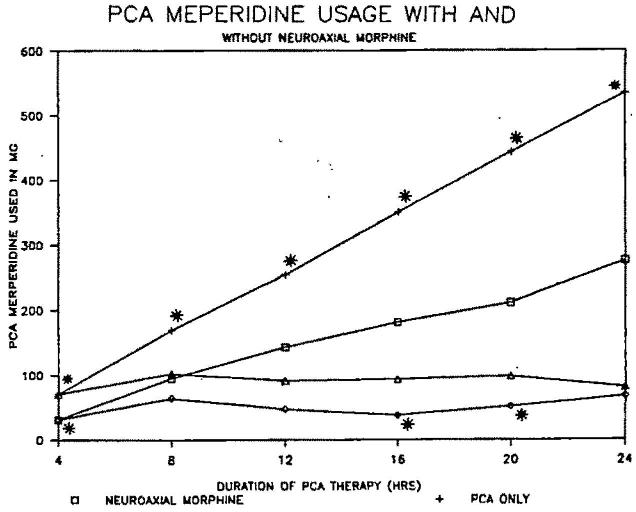

Fig.1: Astrix(*) indicates statistically significance regarding upper 2 lines (cumulative dose), lower 2 non-cummulative

TITLE: TEACHING HYGIENIC PRACTICES OR PRACTICING HYGIENE AS TEACHING?

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INTRODUCTION: The widespread reeducation of personnel regarding hygiene (universal precautions) due to the AIDS epidemic may have missed anesthesia personnel, as many prevailing anesthetic practices appear quite cavalier regarding nosocomial viral transmission, i.e.: the use of **common** syringes and needles for injections to **multiple** patients via intravenous lines throughout the day.[1] We attempted to evaluate whether information alone may be lacking/crucial (a one hour lecture) in effecting changes in clinical technique among university anesthesia personnel.

METHODS: Questionnaires were distributed to personnel attending anesthesia grand round lectures at the University of Pittsburgh. Anonymous responses were collected before and 2 weeks after a lecture addressing anesthetic practices as a possible source of nosocomial infection from 29 and 22 attending personnel, respectively. Questions quantified practices clinically utilized prior to and in the period immediately after the lecture. The 2 week period was chosen, that respondents could report on practices maintained after the lecture. Statistical testing (Chi^2) was applied to answers to detect significance ($P=0.05$).

RESULTS: No significant changes in any anesthetic practices were detected in this study and the following measures continued to be commonly employed: Common syringe techniques (77%), refilling of common syringes from multiple dose vials (MDV) without discarding the MDV subsequently (50%), reuse of MDV opened by unknown persons (72%). The use of common syringes when blood products were administered through the I.V. line occurred infrequently by 23% of personnel. Latex ports and vial rubber stoppers are infrequently cleaned prior to puncture (73%) while needles and drug infusions (86%) (Succinylcholine, Alfentanyl, etc) and single use endotrachial tube stylets (41%) are shared among patients by a large procentage of personnel. One third of all persons continued to believe that changing needles on a common syringe was effective against contamination of the syringe content, inspite of the emphatic presentation of evidence during the lecture to the contrary. While multiple possibilities for crossinfection between patients were routinely noted, the wearing of (self-) protective gloves by personnel while drawing blood, starting IV lines or during mask anesthetics/ intubations was routinely practiced. Nearly 50% of all respondents indicated they felt their anesthetic technique may contribute to nosocomial infection (both surveys). The lecture/information was felt to be useful by 68% and 55% felt the lecture caused a change in technique.

DISCUSSION: The single lecture as a teaching tool was found to have no significant impact on individual hygienic practices in anesthesia, contrary to the respondents overwhelming impression. The didactic quality of the lecture may have been at fault or the methods utilized may have not been sufficiently sensitive to detect changes. Other factors are felt to be more likely by the authors: Most listeners classified the information as useful and subjectively experienced a change in technique. Needle changing as a protective measure against cross infection from common syringes was clearly detailed and emphaticly presented, yet this fact was not assimilated.[2] The presentation of information alone effected no change and may have become lost in the mirad of multiple techniques and daily reality found in anesthetic practice. While universal precautions are a relatively recent and expensive development, cross-utilization techniques may well have a long-standing historical (economical?) background in anesthetic practice. Several respondents in the training process freely commented they used techniques which personally seemed questionable, due to pressures from superiors. Common syringe technique has furthermore been encountered as written policy in one hospital. The widespread use of self-protective gloves prevailed prior to the lecture, probably secondary to massive media coverage of the AIDS epidemic and resultant teaching **and utilization** of this technique. This fact is reassuring, that hygienic techniques can be taught. However, selfprotection may be a superlative motivating factor in this regard. Major hurdles precluding improved levels of hygiene delivered via anesthesia appear to include the lack of systematic education of hygienic practice and clear guidelines from national organizations (CDC/ASA). It appears imperative that extensive education and creation of national guidelines, similar to those protecting health care workers, are needed to protect the patient as well. Questionable techniques are unfortunately extremely prevalent in teaching institutions, as good habits would be most effectively acquired the first time around and poor habits are difficult to break.

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Title: THE PROPHYLACTIC ANTIEMETIC EFFECT OF LORAZEPAM IN ADULTS UNDERGOING OPHTHALMIC SURGERY

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Introduction: The incidence of nausea and vomiting after ophthalmic operations is high. Nausea and vomiting may lead to surgical complications, as wound dehiscence, prolapse of the iris or intraocular bleeding. Also, nausea and vomiting lead to patient's discomfort, distress and prolongation of recovery time. Droperidol is commonly used as an antiemetic, but it may lead to dysphoria, excitatory disturbances of the extrapyramidal system, hypotension, tachycardia and/or prolonged recovery. Lorazepam had been used as an antiemetic in cancer patients who are on chemotherapy. Lorazepam was used as the sole antiemetic[1] or in conjunction with other antiemetics[2]. The objective of this study is to evaluate the prophylactic use of lorazepam as an antiemetic in adult inpatients scheduled for elective ophthalmic operations under general anesthesia.

Methods: After institutional approval and obtaining patients' informed consents, 92 patients age 42 ± 25 years, class I, and II ASA physical status classification, participated. The study was double blinded and the patients were randomized into one of three groups. The patients in group one (N=26) received droperidol (D) 1.25 mg., those in group two (N=28) received lorazapam (L) 0.5 mg., and the patients in group three (N=28) received placebo (P).

In the O.R., after applying the standard monitors, general anesthesia was induced by 1.5 μg/kg of Fentanyl I.V., a sleeping dose of sodium pentothal, NO_2 60%, and isoflurane in oxygen. Vecuronium bromide was used to facilitate orotracheal intubation. The study drug was then given I.V., before the start of surgical manipulation. No other narcotics, sedatives or antiemetics were given. Ventilation was mechanically controlled, aiming at end tidal CO_2 of 4%. At the end of surgery the stomach contents were aspirated and neuromuscular blockade was reversed, using glycopyrrolate and neostigmine. The patients were extubated under deep level of anesthesia.

Nausea and vomiting were evaluated in the recovery room and on the floor, by designated nurses, following a nausea, vomiting scale and a sedation scale. The nausea, vomiting scale was 0=none, 1=nausea, 2=retching, 3=vomiting. If a patient had a scale >0, a repeat dose of the study drug was given I.V. If the nausea and vomiting persisted, promethazine was given. Meperidine was administered for pain relief. The time necessary for post anesthetic recovery and the duration the patient needed to stay in the recovery room were rated.

Results: There was no significant difference among the groups regarding age, weight, duration of anesthesia or duration of surgery (1 way ANOVA). The recovery time and the durations the patients stayed in the recovery room were not significantly different among the groups. (1 way ANOVA) (Table 1)

The number of patients who developed nausea only or nausea and vomiting in the recovery room and on the floor for the first three hours were not significantly different between the groups, but it was significantly ($p < 0.05$) less in the lorazepam group compared to the placebo group, on the floor for the rest of the first postoperative day. (Chi-square) (Table II)

Table I

Group	D	L	P
Number	26	28	28
Recovery time (min) (mean ± SD)	28±25	31±19	23±14
R.R. stay (min) (mean ± SD)	77±39	77±29	81±36

Table II

The Number of Patients Who Developed Nausea and Vomiting (N&V)

Group	D	L	P
Number	26	28	28
N&V in R.R.:	7(27%)	6(21%)	10(36%)
N&V on the floor:			
first 3 hrs.	9(35%)	10(36%)	10(36%)
rest of the day	8(31%)	5(18%)*	11(39%)

*significant at $p < 0.05$

Discussion: We recommend the use of a small dose (0.5mg.) of lorazepam as an antiemetic in adult patients who undergo ophthalmic operations under general anesthesia, as it significantly decreases the incidence of delayed nausea and vomiting and it does not delay recovery.

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Title: THE EFFECT OF THE DURATION OF HYPERVENTILATION DURING ANESTHESIA
ON CARBON DIOXIDE ELIMINATION IN DOGS

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Introduction: Prolonged passive hyperventilation, which is common during neurosurgical anesthesia, depletes the carbon dioxide stores of the body. Fahri and Rahn postulated a continuing loss of carbon dioxide from the body stores for the duration of hyperventilation and the need for a relatively prolonged period of hypoventilation to replace these lost stores (1). Passive hyperventilation has been shown to increase oxygen consumption and, concomitantly, carbon dioxide production; and these changes are proportional to the magnitude of alkalosis produced (2). The purpose of this study was to determine the effect of prolonged hyperventilation on carbon dioxide elimination, thus determining both carbon dioxide production and the loss of body carbon dioxide stores, i.e., carbon dioxide washout.

Methods: Twelve dogs were studied in accordance with the university guidelines for animal care. The dogs were anesthetized with sodium pentobarbital, 30 mg/kg iv, and then maintained with a continuous infusion, 0.2 mg/kg/min. The trachea was intubated with a large bore endotracheal tube, the cuff inflated to give an airtight seal and the animals ventilated with room air, a non-rebreathing system and a constant volume respirator. The expired gas was collected in a modified Med-Science servo-spirometer with selenoid valves. At the end of each spirometer fill, the collected expired gas was sampled by a Varian MAT M3 mass spectrometer. The mass spectrometer was calibrated with two known gas mixtures at each cycle. The analog output signals from the spirometer and the mass spectrometer were digitized and fed into an on-line PDP-11 computing system. Minute ventilation ($\dot{V}E$) and carbon dioxide elimination ($\dot{V}CO_{2R}$) were computed on a minute-to-minute basis. Mixed venous and arterial blood samples were obtained from catheters placed in the pulmonary and femoral arteries, respectively. For the control period $\dot{V}E$ was adjusted to achieve an arterial pH of 7.4 and then kept constant for one hour. The animals were then hyperventilated for six hours, increasing the $\dot{V}E$ in a single step from 5.03±0.02 to 14.41±0.04 L BTPS/m^2/min. When carbon dioxide elimination equals carbon dioxide production a steady state is achieved. Using this steady state value of carbon dioxide production, carbon dioxide washout was calculated. Statistical analysis was by ANOVA; $P<0.05$ was considered significant. Values given are mean ± SEM.

Results: At the end of one hour of hyperventilation, pHv increased from 7.38±0.02 to 7.63±0.03 and was 7.65±0.04 at the end of six hours. $PvCO_2$ decreased from 36.9±2.5 to 15.9±1.2 mm Hg at the end of one hour and at the end of six hours was 15.6±1.3 mm Hg. During the control period, $\dot{V}CO_{2R}$ was 99±5 ml STPD/m^2/min. At the end of the first hour of hyperventilation $\dot{V}CO_{2R}$ increased to 120±7 ml STPD/m^2/min and at the end of six hours of hyperventilation was unchanged at 119±8 ml STPD/m^2/min. All values at the end of one hour of hyperventilation were significantly different from those during the control period ($P < 0.05$); however, there was no significant difference between one and six hours of hyperventilation. The carbon dioxide washout was 2.49±0.04 ml/kg/Δmm Hg $PvCO_2$ at the end of one hour of hyperventilation and was unchanged after six hours of hyperventilation.

Discussion: At the end of one hour of hyperventilation, $\dot{V}CO_{2R}$ equaled carbon dioxide production and thus a steady state was achieved. Beyond this first hour, carbon dioxide stores played no further role in carbon dioxide elimination. In a representative study (Fig), the dog weighed 13.5 kg, $PvCO_2$ decreased from 35 to 14 mm Hg, carbon dioxide washout was 2.45 ml/kg/Δmm Hg $PvCO_2$. At the end of one hour of hyperventilation 695 ml of carbon dioxide were washed out, and as no further change in $\dot{V}CO_{2R}$ occurred, no more carbon dioxide was available to be washed out in the five subsequent hours of hyperventilation. After cessation of hyperventilation, a period of hypoventilation must ensue to replenish the carbon dioxide stores; and the duration of this period will be the same whether hyperventilation was maintained for one hour or for many hours. In conclusion, following hyperventilation, with its consequent depletion of carbon dioxide stores, the duration of hypoventilation needed to replenish these stores will be independent of the duration of the prior hyperventilation providing it has lasted for longer than one hour.

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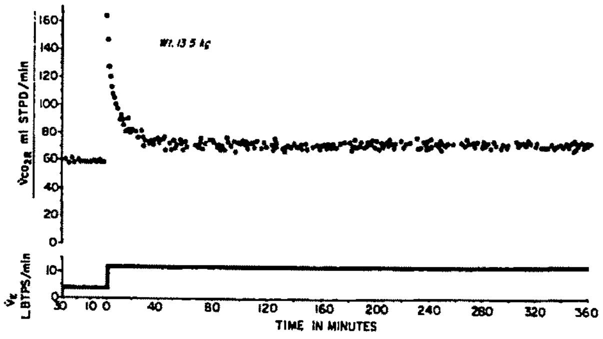

Title: PREVENTION OF PREINDUCTION HYPOKALEMIA BY BETA-2 BLOCKADE

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Introduction. Considerable controversy surrounds the risks and appropriate responses to perioperative hypokalemia. Clinicians frequently cancel surgery or administer intravenous potassium when perioperative serum potassium is below an arbitrary level, usually 3.5 mEq/L. We have previously examined the relationship between preoperative potassium routinely obtained 1-2 days prior to surgery, and intraoperative potassium sampled immediately prior to induction (1). Despite normal preoperative potassium levels, preinduction potassium was lower than preoperative potassium in 44 of 47 patients, and 23 were considered hypokalemic ($K^+ \leq 3.5$ mEq/L). This acute change in serum potassium suggested intracellular potassium uptake rather than systemic depletion.

It is well known that cellular potassium uptake is mediated by β_2 adrenergic receptors, and that circulating epinephrine concentrations are elevated in the perioperative period. The purpose of the present investigation was to test the hypothesis that preinduction hypokalemia is mediated by stimulation of β_2 receptors, possibly by stress-related catecholamine release.

Methods. Institutionally-approved informed consent was obtained from 38 patients undergoing anesthesia for elective surgery. Patients receiving chronic β- or calcium channel blockers, and those with renal failure, LVH, CHF or bradycardia were excluded from study. Patients were randomly assigned to receive propranolol (40 mg orally), atenolol (25 mg orally) or no β blocker (control) at 0530, prior to surgery scheduled for 0800. No other anesthetic premedication was administered. Upon arrival in the operating room, a venous blood sample was obtained for serum potassium measurement. This preinduction potassium concentration was compared to that obtained during routine preoperative testing (37 ± 25 hr earlier). Results were compared by analysis of variance, and expressed as the mean ± standard deviation. Significance was established at $p < 0.05$.

Results. Patient characteristics are shown in the Table. There were no significant differences in age, baseline heart rate, or mean serum potassium between the three groups. Figure 1 compares preoperative and preinduction heart rates for the three groups. Adequacy of β-blockade was determined from preinduction heart rate, which was significantly and similarly decreased in the two treatment groups. In the control group, mean preinduction serum potassium was significantly less than mean preoperative potassium. Individual levels were lower in 11 of 13 patients. In patients pretreated with propranolol, there was no significant change in preinduction potassium compared to preoperative potassium (significantly different from control, $p < 0.05$). In the atenolol group, the decrease in preinduction potassium was intermediate between that of control and propranolol, but did not achieve statistical significance.

Discussion. Serum potassium measured immediately prior to induction of anesthesia was significantly lower than serum potassium measured 1-2 days preoperatively, confirming our previous results. This acute reduction in serum potassium was entirely abolished by the mixed β_1/β_2 antagonist propranolol. The reduction in serum potassium was not however prevented by the selective β_1 antagonist atenolol. These results suggest that preinduction hypokalemia is mediated by β_2 receptor stimulation, most likely by stress-related catecholamine release. The partial effect of atenolol is consistent with its weak β_2 activity.

The results of this study support our previous findings that perioperative potassium measurements may not provide an appropriate basis for decisions regarding cancellation of surgery or potassium therapy. Preinduction hypokalemia may reflect perioperative stress.

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TABLE

	Control	Atenolol	Propranolol
patients	13	12	13
age (yr)	58 ± 18	58 ± 11	62 ± 10
preop HR (min^{-1})	78 ± 13	75 ± 16	77 ± 10
serum K^+ ($mEq \cdot L^{-1}$)	4.4 ± 0.3	4.2 ± 0.3	4.1 ± 0.4

There were no significant differences between groups.

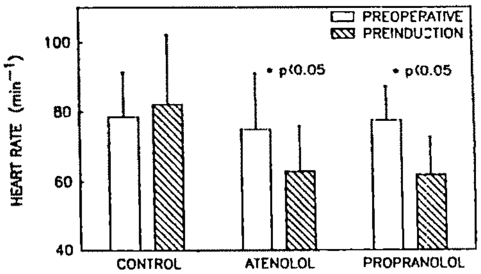

FIGURE 1: Preoperative and preinduction heart rates.

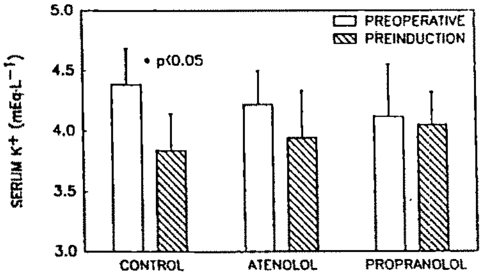

FIGURE 2: Preoperative and preinduction serum potassium.

*Preinduction significantly different from preoperative ($p < 0.05$).

Title: BLOOD FLOW DISTRIBUTION DURING CONTROLLED HYPOTENSION INDUCED BY FENOLDOPAM IN ANESTHETIZED DOGS

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Introduction. Recently fenoldopam (F) has been advocated as a hypotensive agent because of its effectiveness in lowering blood pressure and preserving renal perfusion.[1] The F-induced vasodilation is mediated by stimulation of dopamine 1 receptors.[2] The presence of these receptors in the cerebral, coronary, mesenteric and other vascular beds suggests that vasodilation may not be limited to the kidney, however, supporting data are lacking. The purpose of this study is to measure blood flow distribution during controlled hypotension induced by F and compare its effects to those of nitroprusside (NP).

Methods. Eight mongrel dogs anesthetized with 1.00% halothane in O_2 were studied. A catheter was placed in the descending aorta via a femoral artery for reference flow sample and blood pressure measurement. Cardiac output was measured using a pulmonary artery catheter and thermodilution technique. The left ventricle (LV) was instrumented to examine the pressure-diameter relationship for the assessment of cardiac contractility. Radioactive microspheres were injected into the left atrium for blood flow measurement. Following the first baseline measurement, either F or NP was infused to lower mean blood pressure by 30%. Measurement was repeated after 40 minutes of hypotension. A 60 minute period was allowed for recovery between the two drugs. The sequence of microspheres and the order of F and NP were alternated randomly so each dog served as its own control. Data were compared between baselines, F and NP using analysis of variance and paired t-test with $p < .05$ considered significant. Values are expressed as means ± standard error of mean. This study was approved by the institutional Animal Care Committee.

Results. Table 1 shows the effects of F and NP on organ blood flow. Hepatic arterial flow increased 65% during NP infusion and decreased 55% with F. Blood flow to the brain, heart, intestine and skin was unchanged, whereas splenic flow decreased 40% during hypotension produced by either drug. In contrast to NP, F increased blood flow to the renal cortex by 22%. At an equal reduction in arterial blood pressure, NP produced larger decreases in LV end diastolic pressure and wall stress, the changes in cardiac rhythm, output and contractility were not statistically significant.

Discussion. Maintenance of normal perfusion to vital organs during controlled hypotension is a major concern. In this study, hypotension induced by F was rapid and stable. Importantly, blood flow to the brain and heart was well maintained, whereas renal blood flow increased significantly in spite of a reduction in perfusion pressure. The improvement in renal perfusion was probably at the expense of the splenic and peripheral beds. However, the decrease in hepatic arterial flow with F may result from portal venous vasodilation caused by this dopamine 1 receptor agonist. The results show that F is an effective agent for controlled hypotension that compares favorably to NP, particularly when renal perfusion should be maintained.

References.
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Table 1: Organ Blood Flows (ml/min/100gr)

	Baseline 1	NP	Baseline 2	F
Brain	56.8± 5.4	56.6± 3.4	54.6± 4.7	50.2± 4.5
Heart	71.5± 7.4	75.8± 6.9	71.0± 8.4	70.5± 4.2
Kidney	680.6±37.1	567.3±34.8*	686.1±52.1	838.3±30.1^{*+}
Liver	14.7± 3.8	24.5± 4.8*	13.8± 4.5	6.4± 1.9^{*+}
Spleen	198.0±34.3	123.8±11.0*	226.3±20.0	127.6± 9.1*
Intestine	60.5± 6.9	63.2±10.5	66.4± 4.7	76.1± 9.7
Muscle	4.7± .34	5.3± .5	4.5± .6	3.1± .3^{*+}

$^{*}p < .05$ compared to baseline, $^{+}p < .05$ compared to NP

Title: THE EFFECT OF HEPARIN ON THE RELATIONSHIP BETWEEN CARDIOVASCULAR HEMODYNAMICS AND IONIZED CALCIUM

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Introduction: Intravenous administration of heparin has been shown to lower mean arterial pressure (MAP) by reducing systemic vascular resistance (SVR)[1,2]. Furthermore, it has been previously reported that heparin binds serum ionized calcium ([Ca^{++}]) in vivo.[3] We hypothesized that, via the mechanism of calcium binding, heparin adminstration could affect myocardial contractility. The purpose of this study, therefore, was to evaluate the influence heparin, administered at various rates, has upon the levels and relationship between cardiovascular hemodynamics and [Ca^{++}].

Methods: This study received institutional approval, and informed consent was obtained from each subject. Patients undergoing coronary artery bypass grafting having a preoperative left ventricular ejection fraction greater than 40% documented on angiography were eligible to participate. Anesthesia was induced with intravenous sublimaze (53.43 ± 1.44 ug/kg) and vecuronium (0.14 ± 0.01 mg/kg) and maintained with a continuous infusion of sublimaze (10.56 ± 0.29 ug/kg/min) and, if required, inhalation agent.

Part 1 of the study was double-blinded and compared the hemodynamic response and changes in [Ca^{++}] resulting from the administration of heparin or placebo (saline). Two groups of eight patients each received either intravenous heparin 400 units/kg or an equivalent volume of normal saline over 1 minute.

Part 2 of the study was not blinded and looked at hemodynamic and [Ca^{++}] changes brought about by varying the rate of heparin administration. Three groups of ten patients each received intravenous heparin 400 units/kg over either 30 seconds, 1 minute or 2 1/2 minutes.

Prior to administration of heparin or placebo, all surgical stimulation was halted. If inhalation agent was in use, inspired and expired concentrations of the agent, as measured by mass spectrometry, were required to be within 10% of each other. Once a hemodynamically steady state was established (minimum of 5 minutes), the following parameters were measured and recorded; MAP, mean pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), central venous pressure, cardiac output (CO) by thermodilution technique, pulse, and [Ca^{++}]. Heparin or placebo was then administered through a central venous line. Measurements of hemodynamic parameters and [Ca^{++}] were repeated at one, three, five and seven minutes following drug administration.

Baseline values were compared via a one-way analysis of variance in conjunction with the Student-Newman-Keuls multiple comparisons procedure. Changes over time within each group were examined by an analysis of variance and changes over time between groups were examined by a multivariate analysis of variance.

Results: Age, height, weight, body surface area, hematocrit, temperature and baseline [Ca^{++}] did not differ between groups, nor did any of the baseline measured or derived hemodynamic parameters.

Part 1- Patients in the saline group showed no significant change in any measured or derived parameters. Patients receiving heparin showed a statistically significant decrease in MAP, left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR) and [Ca^{++}] at 1 minute after injection. There was no change thereafter.

Part 2- All three groups showed a significant and equal decrease in MAP, LVSWI, SVR and [Ca^{++}] by 1 minute after injection which, as in part 1, did not subsequently change.

Discussion: Intravenous heparin (400 units/kg) administration resulted in a decrease in MAP, in part, due to a decrease in SVR. Since LVSWI decreased, and CO did not increase, in the face of a constant PCWP and lower SVR, we conclude that a myocardial depressant effect was also associated with the response to heparin. Finally, the decrease in [Ca^{++}] coincided directly with the decrease in LVSWI, independent of heparin administration rate. Therefore, the hemodynamic response to intravenous heparin may be calcium induced and not a direct effect of the drug itself.

References:

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3. Urban P, Scheidegger D, Buchmann B, Skarvan K. The hemodynamic effects of heparin and their relation to ionized calcium levels.
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Table 1. Baseline and 1 Minute Postinjection Parameters

	[Ca^{++}] (mmol/L)	MAP (mm Hg)	SVR (dyn.s.cm^{-5})	LVSWI (g.M/M^2/bt)
PART 1.				
Heparin				
preinjection	1.25 ± .17	75.6 ± 13.6	1569 ± 413	30.1 ± 6.5
postinjection	1.21 ± .06**	66.9 ± 3.7**	1351 ± 407**	26.9 ± 6.2**
Saline				
preinjection	1.26 ± .03	74.3 ± 7.4	1309 ± 296	32.6 ± 12.2
postinjection	1.27 ± .03	74.5 ± 6.5	1332 ± 274	31.4 ± 10.8
Part 2.				
30 sec administration				
preinjection	1.30 ± .09	78.6 ± 10.6	1333 ± 366	39.3 ± 8.9
postinjection	1.27 ± .10**	69.3 ± 12.0**	1152 ± 375**	33.8 ± 8.7**
1 min administration				
preinjection	1.24 ± .06	76.3 ± 7.9	1561 ± 417	31.0 ± 11.0
postinjection	1.20 ± .06**	68.6 ± 8.2**	1346 ± 370**	27.4 ± 8.9**
2$^{1/2}$ min administration				
preinjection	1.25 ± .06	80.2 ± 8.5	1434 ± 313	35.1 ± 11.0
postinjection	1.21 ± .06**	68.7 ± 6.8**	1217 ± 211**	29.8 ± 11.9**

mean + SD, $^{**}p < 0.05$

Title: **IS BENZODIAZEPINE-BARBITURATE ANESTHETIC SYNERGISM ONE-SIDED? A STUDY IN RATS**

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Introduction: Barbiturates allosterically enhance benzodiazepine binding to the benzodiazepine receptor (1), and this binding enhancement manifests itself in the form of pentobarbital-induced potentiation of the benzodiazepine hypnotic action. A midazolam (diazepam)-pentobarbital (thiopental) combination has been found to result in a synergistic (supra-additive) hypnotic interaction both in humans and in rats (2,3). Benzodiazepines may have an allosteric effect on barbiturate binding sites as well and, therefore, potentiate the barbiturate hypnotic action. The aim of the present study was to determine whether midazolam-pentobarbital synergism is one-sided.

Method: Male Sprague-Dawley rats (225-275 g) were used for the study, which was approved by the Institutional Animal Investigation Committee. Loss of the righting reflex was used as an index of hypnotic action. Two series of experiments were performed. In one series, shifts in the midazolam dose-response curve along the dose axis under the influence of small doses of pentobarbital were determined. In another series, changes in the pentobarbital dose-response curve caused by small doses of midazolam were determined and compared with the results of the first series of experiments. Each series of experiments consisted of three subseries (see Table 1): one with an agent given alone (plus saline) and two with the addition of another component of the combination in a fixed dose representing 1/30 or 1/10 of its hypnotic ED$_{50}$ value determined in previous experiments. Four or five groups of four animals were used to determine the dose-response curve in each subseries of experiments. Each animal was given only one predetermined dose of an agent or a combination of the agents which were injected into the saphenous vein over 15 seconds. The righting reflex test was determined 5 minutes following the injection of the agent or a combination of the agents. ED$_{50}$ values were determined with a probit procedure, and statistical significance of the shifts in ED$_{50}$ doses were established by a t-test.

Results: The hypnotic ED$_{50}$ value for midazolam, 5.9 mg·kg^{-1} was profoundly decreased by pentobarbital: to 1.4 mg·kg^{-1} ($p<0.001$) with a dose equal to 1/30 of the pentobarbital hypnotic ED$_{50}$ value and 0.8 mg·kg^{-1} ($p<0.0001$) with 1/10 of the pentobarbital ED$_{50}$ value. The hypnotic ED$_{50}$ value for pentobarbital, 11.7 mg kg^{-1} was also profoundly decreased by midazolam: to 3.8 mg·kg^{-1} ($p<0.001$) and 1.7 mg·kg^{-1} ($p<0.0001$) with the doses equal to 1/30 and 1/10 of the midazolam ED$_{50}$ value, respectively. The comparison of changes in potency (see Tables 1 and 2) shows that midazolam potentiates the hypnotic effect of pentobarbital to the same extent as pentobarbital potentiates hypnotic effect of midazolam.

Discussion: Our data reject the hypothesis of one-sided benzodiazepine-barbiturate anesthetic synergism. Strong midazolam-induced potentiation of the hypnotic effect of pentobarbital suggests that midazolam may allosterically enhance the interaction of pentobarbital with barbiturate binding sites. The study of the effect of benzodiazepines on the barbiturate binding will be performed to confirm this suggestion.

Table 1. Effect of pentobarbital on midazolam ED$_{50}$ value for loss of the righting reflex (Series 1).

Subseries†	Dose of pentobarbital in mg·kg^{-1}	Midazolam ED$_{50}$ in mg·kg^{-1} (95% conf. limits)	Potency
1	None	5.9 (2.2, 12.9)	1.0
2	0.4 (1/30)*	1.4 (0.1, 3.5)	2.4 $p<0.001$
3	1.2 (1/10)*	0.8 (0.3, 1.7)	13.5 $p<0.0001$

* - Fraction of hypnotic ED$_{50}$ for pentobarbital. † - 16-20 animals in each subseries. The p value for the difference from subseries 1.

Table 2. Effect of midazolam on pentobarbital ED$_{50}$ value for loss of the righting reflex (Series 2).

Subseries†	Dose of midazolam in mg·kg^{-1}	Pentobarbital ED$_{50}$ in mg·kg^{-1} (95% conf. limits)	Potency
1	None	11.7 (10.6, 12.7)	1.0
2	0.2 (1/30)*	3.8 (1.6, 5.1)	3.3 $p<0.001$
3	0.6 (1/10)*	1.7 (1.0, 2.3)	14.6 $p<0.0001$

Abbreviations are the same as in Table 1.

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This work was supported by NIH grant, GM39344.

Title: **BLOCKADE OF NOCICEPTIVE INPUT DURING SURGERY CAN DECREASE POSTOPERATIVE PAIN**

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Introduction: The aims of the present study were to determine: (1) whether local anesthesia used during surgery decreases the severity of pain beyond the immediate postoperative period, when the pain relief cannot be explained by prolonged presence of the local anesthetics in the body; and (2) whether spinal anesthesia (which does not provide a significant direct effect of a local anesthetic on tissues in the area of surgery) relieves postoperative pain similar to local anesthesia.

Methods: This is a randomized double-blind study with approval from the Institutional Human Investigation Committee and informed consent from the patients. Thirty-six male patients, scheduled for elective inguinal hernia repair (Basini technique) were divided into three groups: general anesthesia (G), general plus local anesthesia (G + L), and spinal anesthesia (S), with 12 patients in each group. In the G group, anesthesia was induced with thiopental (4 $mg\cdot kg^{-1}$), and tracheal intubation was performed with the aid of succinylcholine (1 $mg\cdot kg^{-1}$). After intubation, pancuronium (5 mg) was given, with additional doses (1 mg) as indicated during surgery. Anesthesia was maintained with N_2O/O_2 (2:1), and halothane 0.5%. No narcotic was used for premedication or during surgery. In the G + L group, in addition to the general anesthesia performed as described above, the infiltration of the abdominal wall with 0.25% bupivacaine (40 cc) along the line of the proposed incision was made 5 minutes before the surgery. In the S group, under conscious sedation with midazolam (0.07 $mg\cdot kg_{-1}$, i.v.), the subarachnoid block was performed with 0.5% solution of bupivacaine (12.5 mg). The patients from all three groups received identical postoperative pain treatment. When a patient complained of pain, he received meperidine, 50 mg, i.m. After the first injection, each patient received meperidine, 25 mg, every 4 hr on the first and every 6 hr on the second day after surgery regardless of pain level. Starting with the third day, the patients received acetaminophen, 500 mg, every 4 hr, orally. The severity of constant incisional pain, movement-associated incisional pain, and pain upon pressure on the surgical wound were assessed with a visual analog self-rating method at 24 hr, 48 hr, and 10 days following surgery. The movement-associated incisional pain was assessed when the patient got out of the bed. An algometer with a pressure surface of 4 cm^2 was used for the determination of the pain on pressure. A one-way analysis of the variance and the Fisher's protected least significant difference test were used for statistical validation.

Results: The most dramatic effect of local and spinal anesthesia was observed with regard to the constant incisional pain. In the G + L group, this type of pain was practically abolished both 24 hr and 48 hr after surgery at a time when the pain intensity score in the G group was 44 ± 5 and 32 ± 5, respectively ($p<0.0005$ from G + L). In the S group, the constant pain score (19 ± 5 and 10 ± 2, respectively) was much lower than in the G group ($p<0.0005$) and not statistically different from the G + L group (Figure 1). The score of the movement-associated incisional pain at 24 hr was the highest in the G group (72 ± 5) and the lowest in the G + L group (16 ± 3, $p<0.0005$ from G); the S group occupied the intermediate position (40 ± 6, $p<0.002$ from G). At 48 hr, the movement-associated pain scores were proportionally decreased in the G and S groups without any significant change in the G + L Group. Pain intensity upon pressure on the wound also was highest in the G group and lowest in the G + L group, with the S group in the intermediate position, both at 24 hr and 48 hr. Ten days after surgery, the difference between the G and the G + L groups still was present (pain score 35 ± 4 vs. 16 ± 3, $p<0.01$, with 0.6 kg/cm^2 pressure). At the same time, no difference was found between the G and S groups.

Discussion: Our results indicate that postoperative pain in inguinal herniorrhaphy can be decreased profoundly if the surgery is performed with the addition of local to general anesthesia or the use of spinal anesthesia. Recent experimental data indicate that nociceptive impulses may set off a prolonged increase in spinal cord excitability (1). We hypothesize that neural blockade, by preventing nociceptive impulses from entering the CNS during and immediately after surgery, suppresses the formation of the sustained hyperexcitable state in the CNS, which is responsible for the maintenance of postoperative pain.

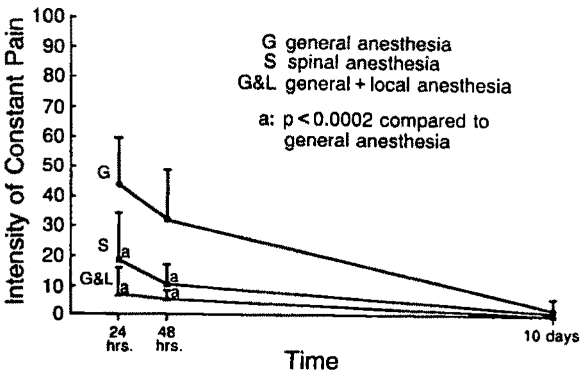

Figure 1. Intensity of constant incisional pain with three different types of anesthesia. The pain score is presented in mm on 100-mm visual analog scale (mean ± SEM).

References.:

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Title: ENHANCEMENT OF 0.125% BUPIVACAINE SENSORY BLOCK BY LOW DOSE PHENOL IN RAT SCIATIC NERVE

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Introduction: The use of local anesthetics for nerve block in patients with persistent pain is a well-established technique, but the duration of pain relief is short and the patient must endure repeated procedures to maintain it. We propose to combine a local anesthetic with a sub-neurolytic concentration of phenol. The combination of 2 substances may provide longer pain relief than a standard local anesthetic. In addition, the nerve block should be reversible and no neurological sequelae should follow when these compounds are used.

Materials and Methods: Thirty (30) albino rats, each weighing 210-290 grams, were utilized with the approval of the Institutional Animal Care and Use Committee of our facility. 0.125% Bupivacaine (BPV), 0.5% Phenol (PH), and a combination of the two were used on 3 groups of 10 rats each. The experiment was performed on a double-blind basis. These solutions were injected into the lower extremity of the rats in the area under the skin at the junction of the biceps femoris and gluteus muscles. The sciatic nerve was infiltrated in the mid-thigh with weight-adjusted doses (0.3 ml. of solution/225 g. of body wt.). All animals were injected in the left leg by the same person using tuberculin syringes and 26 G, ½ inch needles. A control solution of normal saline was injected into the contralateral extremity. The rats were observed for 330 minutes at 30 minute intervals for motor and/or sensory blockade. Only sensory changes were quantified. Analgesia was evaluated with a thermostatic hot plate (THERMAJUST, Technolabs).[1] The temperature was set at 51°C. Scores from zero to 3 were given according to the hind paw licking pattern with right (R) and left (L) responses as follows: A sequence of R.R.R.=3; R.L.R., R.R.L., or L.R.R.=2; R.L.L.=1; and all other sequences=0. The area under the time-effect curve for BPV, PH, and BPV+PH was determined for each animal. Analysis of variance among the groups and pairwise comparisons between the groups were applied using Bonferroni corrections.

Results: Fig. 1 presents the means and standard errors of the means for the intensity of sensory block for each treatment group at 30 minute intervals. The calculations for the full group of 30 rats and a second calculation for 26 rats, excluding 4 non-responders, are listed. The latter were distributed among all treatments and represented animals which showed no motor or sensory block and may have represented failed approximation of the nerve. The data for the area under the time-effect curves (AUC) for all animals (Table 1) was analyzed by treatment group using analysis of variance and revealed a statistically significant difference among the groups ($p<0.01$). Pairwise comparisons are presented in Table 2 along with a second analysis of the data which excluded non-responders (analysis of variance of the 26 rats was also significant, $p<0.01$).

Discussion: The combination of 0.125% BPV and 0.5% PH resulted in a greater sensory block than either agent alone. In addition to a greater peak intensity of block, the duration of sensory block was approximately doubled (Fig. 1). The data of Table 1 strongly suggest that the effects of BPV and PH are additive in terms of sensory block. Pairwise comparisons between treatment groups demonstrated that 0.125% BPV was no different in effect than 0.5% PH (Table 2). In both the full group and the group minus non-responders, BPV+PH was significantly more effective than PH alone. In the comparison between BPV+PH and BPV, the full group showed marginal significance (93% certainty of greater effect with the combination) while high significance was found in the comparison which excluded non-responders. All motor and sensory effects reversed with time and no evidence of nerve damage was seen with the injection of the active agent or the control.

Figure 1. Sensory Score versus Time (min.)

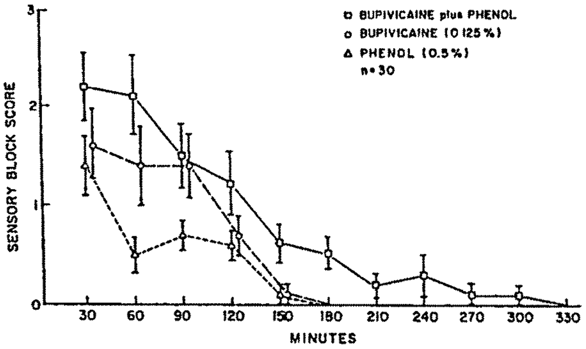

Table 1.

AREAS UNDER TIME-EFFECT CURVES (AUC*) FOR BPV (0.125%), PH (0.5%), AND BPV+PH

	BPV		PH		BPV+PH	
	n=30	n=26	n=30	n=26	n=30	n=26
Mean	130	150	75	94	227	252
S.E.	±26	±24	±17	±15	±33	±24

AUC* = Score x Minutes

Table 2.

PAIRWISE STATISTICAL COMPARISONS OF AUC BETWEEN TREATMENT GROUPS

	t		p	
	n=30	n=26	n=30	n=26
BPV vs. PH	1.612	1.795	N.S.	N.S.
BPV+PH vs. PHENOL	4.07	5.04	0.01	0.005
BPV+PH vs. BPV	2.459	3.346	0.07	0.01

References:

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TITLE: A NEW NONFERROMAGNETIC VENTILATOR FOR USE DURING MAGNETIC RESONANCE IMAGING

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Introduction. Most conventional ventilators today have ferromagnetic parts and, therefore, cannot be near a magnetic resonance imager (MRI) because magnetic current interferes with the mechanics and the electronics used for ventilator controls and alarms. The ventilator itself could interfere with the radio frequencies of the MRI and thus distort the image. This report describes specifications of a newly constructed, totally nonferromagnetic ventilator.

Methods. The nonferromagnetic ventilator is lightweight and portable and can be set within the bore of the MRI as well as outside it without interfering with imaging. An internally adjustable, spontaneous flow mechanism allows this ventilator to be used for patients of all sizes, from neonates to adults, a feature not found on commercial ventilators currently being marketed for use in MRI. F_IO_2 with this ventilator depends totally on the source gas. There is a totally pneumatic, low-pressure alarm, which also acts as a disconnect alarm during continuous positive airway pressure > 5 cm H_2O. There is also an adjustable, high-pressure alarm.

Results. The ventilator was tested in-vitro with a lung model (Vent Aid Training Test Lung) (Table). Also, the ventilator has been used successfully for ventilation of 4 anesthetized patients undergoing MRI.

Discussion. Our ventilator meets current needs in the MRI environment. Ventilation of patients who undergo MRI requires either controlled or spontaneous ventilation with a modified Bain circuit or a circle system, or a nonferromagnetic mechanical ventilator.

Table. Capabilities of a New Nonferromagnetic Ventilator

Ventilator Specifications	Specification Limits Minimum	Maximum
Inspiratory time (sec)	0.4	3.0
Rate (breaths/min)	0	150
Inspiratory flow (L/min)	< 6	120
Pressure limit (cm H_2O)	5	110 (internal)
Continuous positive airway pressure (cm H_2O)*	0	20
Alarm delay†	5.5 sec	2.16 min
Alarm sensitivity	off	> 100 cm H_2O
Spontaneous flow (L/min)‡	10 or 30§	75

*Adding water to the Emerson exhalation valve will alter these values.
†This refers to the minimum pressure needed to auto reset the alarm.
‡This occurs only during the expiratory phase; therefore tidal volume will not be altered.
§Internally adjustable--allows for pediatric application.

Title: HYPOXIC PULMONARY VASOCONSTRICTION AND SHUNT DURING PULMONARY RESECTIONS

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Introduction. Hypoxia during one-lung ventilation (1 LV) is still a clinical issue (1). The purpose of our study was to examine if there are any differences before starting 1 LV and during 1 LV between patients who develop hypoxia and who do not.

Methods. 30 patients, ASA risk group II - III, scheduled for pulmonary resections, gave their written informed consent to participate in this institutionally approved study. Hemodynamic monitoring was established with a radial arterial and a pulmonary artery catheter. Anesthesia was standardized (1 MAC enflurane). Ventilation via a left Bronchocath double lumen-tube was controlled with a $FiO_2 = 1.0$, and a tidal volume of 10 ml kg^{-1} at a rate to maintain p_aCO_2 within normal range. CPAP/PEEP-ventilation was not applied. Vasoactive drugs were not given. Arterial and mixed venous blood gases, analyzed immediately, and hemodynamic measurements were obtained before induction, during two-lung ventilation (2 LV) in the supine and lateral decubitus position, during 1 LV, and after extubation. Statistical analysis was performed by the Wilcoxon signed rank and rank-sum test.

Results. 8 out of 30 patients developed hypoxia during 1 LV, that means they had a p_aO_2 less than 75 mm Hg (range: 44.5 to 74.8 mm Hg). The results are shown in table 1, 2, and 3.

Discussion. Enflurane is not reported to inhibit hypoxic pulmonary vasoconstriction (HPV) in a clinical study (3), but in an experimental study (4). Pulmonary vascular pressure and p_vO_2, further determinants of HPV, were different between both groups during 1 LV, but MPAP increased in both groups to the same extent in comparison to 2 LV. In our study HPV was inhibited by 25.2 ± 22.9 % in all of our patients, by 20.0 ± 17.0 % in the group with hypoxia, and by 27.0 ± 24.5 % in the patients without hypoxia. Hence, we came to the conclusion that hypoxia is not induced by increased inhibition of HPV. Since inhibition of HPV during 1 LV was not different in both groups, increased preexisting shunt values before starting 1 LV might contribute to the frequency of hypoxia during 1 LV.

Tables. Group A: Patients who developed hypoxia during 1 LV
Group B: Patients without hypoxia during 1 LV

Table 1. Before induction of anesthesia.

(mean ± SD)	Group A	Group B	
p_aO_2	73.0 ± 6.5	76.8 ± 12.0	ns
Q_s/Q_t	3.7 ± 1.1	2.7 ± 1.0	ns
MPAP	15.5 ± 5.9	14.6 ± 5.7	ns
p_vO_2	40.8 ± 4.8	39.8 ± 3.5	ns

Table 2. 2 LV: 20 min. after surgical opening of the chest.

(mean ± SD)	Group A	Group B	
p_aO_2	374.4 ± 81.9	473.2 ± 59.5	$p \leq 0.05$
Q_s/Q_t	32.0 ± 9.9	19.6 ± 7.9	$p \leq 0.001$
MPAP	23.1 ± 8.1	17.8 ± 6.4	$p \leq 0.05$
p_vO_2	50.3 ± 8.0	53.2 ± 9.2	ns

Table 3. 20 min. after collapse of the non-dependent lung

(mean ± SD)	Group A	Group B	
p_aO_2	57.7 ± 9.8	235.6 ± 100.5	$p \leq 0.001$
Q_s/Q_t	44.4 ± 6.3	36.5 ± 7.3	$p \leq 0.01$
MPAP	29.9 ± 9.0	22.3 ± 5.2	$p \leq 0.05$
p_vO_2	37.6 ± 3.9	49.3 ± 6.0	$p \leq 0.01$

p_aO_2 (mmHg): arterial O_2 partial pressure
Q_s/Q_t (%): shunt
MPAP (mmHg): mean pulmonary artery pressure
p_vO_2 (mmHg): mixed venous O_2 partial pressure
ns: not significant

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Title:
USE OF LABETALOL TO CONTROL CARDIOVASCULAR RESPONSES TO ELECTROCONVULSIVE THERAPY

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Introduction. Electroconvulsive Therapy (ECT) is known to produce dramatic increases in circulating catecholamines that can cause considerable hypertension and tachycardia (1). These changes are known to produce myocardial ischemia and may cause myocardial infarction (2). Beta blocking drugs such as propanolol (3) and esmolol (4) have been used to attenuate the tachycardia and hypertension associated with ECT. In this study labetalol, a drug with both alpha and beta adrenergic blocking effects, was used to attenuate both hypertension and tachycardia during ECT.

Methods. After approval by the Human Investigations Committee, informed written consent was obtained from 11 elderly patients (age 53-84) ASA Class II, III and IV. Patients were excluded from the study if they had a history of bronchial asthma, A-V conduction block greater than first degree, or were currently taking a beta blocking drug. A total of 103 ECT treatments were given (56 treatments with labetalol, 47 treatments with placebo). All patients received glycopyrrolate 0.2 mg IM and ranitidine 150 mg PO 30 to 60 minutes prior to ECT. Heart rate (HR) was monitored by a single lead ECG (lead II). Blood pressure (BP) was monitored by manual cuff measurements. Each patient was given 3 mg of d-tubocurare and .625 mg droperidol IV 5 minutes prior to starting ECT. Ninety seconds prior to electrical stimulus, each patient was given either 0.5-1.0 ml of 0.9% saline or labetalol (5 mg/ml) IV in a double-blind cross-over design. Range of labetalol dose was 0.06-0.17 mg/kg. Dosage of labetalol/placebo was determined by the patient's baseline HR (bpm) at the time of each treatment with 0.5 ml given for HR < 80 bpm; 1.0 ml for HR > 81 bpm. Patients with a BP > 150/80 at time of treatment were given 1.0 ml of study drug regardless of HR. Standard anesthetic induction followed with thiopental 1.5-3.7 mg/kg, succinylcholine 1.3-2.7 mg/kg, alfentanil 2.4-8.3 micrograms/kg. Patients were given 100% oxygen by ambu bag and mask with oxygen saturation continuously monitored by pulse oximetry. Baseline HR and BP were obtained 30, 5, 1 minutes before electrical stimulus, immediately before stimulus, and 0.5, 1, 2, 3, 4, 5, 10, and 30 minutes after electrical stimulus. Any cardiac arrhythmias during the treatment such as premature ventricular contractions (PVCs) or premature atrial contractions (PACs) were noted.

Results. In preliminary analyses as compared to placebo, labetalol significantly decreased the mean arterial pressure (MAP) by 11.4mmHg (9%) (P <0.001) at 0.5 minutes and 10.4mmHg (8%) (P <0.001) 1 minute after electrical stimulus. The increase in HR was significantly diminished by 30.6 bpm (23%) (P <0.001) at 0.5 minutes and by 33.1 bpm (26%) (P <0.001) at 1.0 minutes by labetalol compared to placebo. There was a trend to fewer PVCs and PACs in patients receiving labetalol. No bradycardia, hypotension or effect on treatment outcome was noted.

Discussion. This study shows that labetalol appears to be an effective and safe agent to help attenuate the hypertension, tachycardia and, possibly, arrhythmias associated with ECT in elderly patients. Compared to esmolol bolus (1 mg/kg) (4), labetalol (0.05-0.1 mg/kg) is comparable in reducing the increase in HR and BP associated with ECT. The greater hemodynamic stability produced by labetalol or esmolol could help decrease the cardiovascular morbidity and mortality associated with ECT in patients with documented as well as undiagnosed cardiovascular disease.

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Title: N_2O-INDUCED ELEVATIONS IN URINARY FORMIMINOGLUTAMIC ACID (FIGLU) IN AGED RATS

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Introduction. Brief exposures to nitrous oxide (N_2O) markedly inactivate the vitamin B_{12}-dependent enzyme methionine synthase and disrupt the normal pathways of folic acid metabolism. The toxic effects produced by N_2O appear to be greatest in critically ill patients and in those with a pre-existing vitamin B_{12} and/or folic deficiency.[1] The elderly may constitute another subpopulation of patients that are susceptible to the inactivation produced by N_2O, since they are often debilitated and deficiencies in vitamin B_{12} and/or folic acid may occur in as many as 25% of patients over 60 years of age.[2,3] However, since variables such as diet, vitamin intake, disease processes, medications, and duration and type of surgery are difficult to control in the perioperative period, the role of aging *per se* on the N_2O-induced disruption in folic acid metabolism is difficult to examine in the clinical setting. Therefore, in the present study we employed the Fischer 344 rat, a rodent model extensively employed in research on aging, to examine the combined influence of N_2O and age on folic acid metabolism.

The N_2O-induced disruption of folic acid metabolism was noninvasively assessed by measuring the excretion of formiminoglutamic acid (FIGLU) in urine. FIGLU is an intermediate in the metabolism of the amino acid histidine, and the breakdown of FIGLU requires tetrahydrofolate. An increased urinary excretion of FIGLU occurs in mammals with a folic acid deficiency.[4]

Methods. These experiments were approved by the Animal Studies Subcommittee at VAMCSF. Male Fischer 344 rats of 3 different ages [2-month (young; n=8), 12-month (middle-aged; n=8), and 24-month (old or elderly; n=7)] were placed in metabolic chambers for timed collections of urine samples. After obtaining background urine collections before N_2O exposure, rats were given 60% N_2O/40% O_2 for 6 hrs. Following N_2O exposure, rats were returned to their metabolic cages in room air and daily urine samples collected. FIGLU concentrations were analyzed by a spectrophotometric assay.[4] Statistical computations were performed by an analysis of variance.

Results. Prior to N_2O exposure, FIGLU levels in urine were relatively small and did not differ among the 3 different age groups (Fig. 1). Background FIGLU excretion rates (mean ± S.D.) were 1.9 ± 1.9, 1.6 ± 2.0, and 4.5 ± 4.5 nmol/hr in the young, middle-aged, and elderly animals, respectively. Urine collections obtained the day following N_2O exposure showed marked elevations (> 100-fold) in FIGLU excretion rates, which increased with increasing age (old > middle-aged > young; $p < 0.01$) (Fig. 1). FIGLU excretion rates returned to near background levels by the second day after N_2O exposure in all 3 age groups (Fig. 1).

Discussion. The elevations in urinary FIGLU that occur after exposure to N_2O are presumably related to a lowering of tissue tetrahydrofolate levels. The present results suggest that the N_2O-induced depletion of tetrahydrofolate increases with increasing age. However, the abnormally elevated FIGLU levels return to background values by the second day after N_2O exposure. This latter finding implies that the time course of recovery of N_2O-induced folic acid abnormalities is similar in animals of all age groups.

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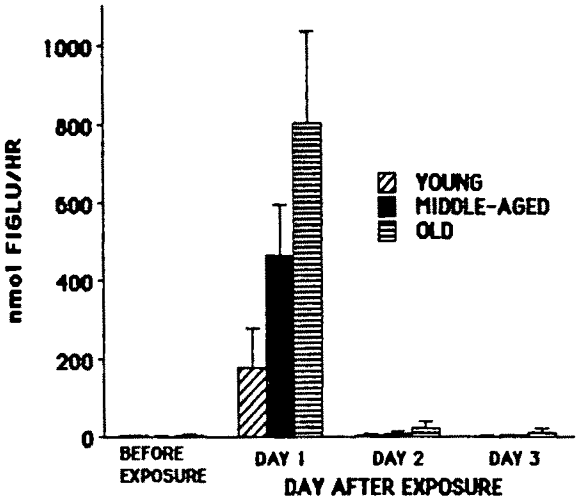

Figure 1. Urinary FIGLU excretion rates (mean ± S.D.) in rats immediately before and on days after exposure to 60% N_2O for 6 hrs. Values before N_2O exposure are small and are barely visible on the graph.

Title: PHARMACOKINETICS OF ALFENTANIL DURING RENAL TRANSPLANTATION IN DIABETIC AND NON-DIABETIC PATIENTS

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Introduction: Although two studies have examined the pharmacokinetics of alfentanil in patients with chronic renal failure, their results are conflicting. One reported only an increase in the Vdss compared to normals[1] while the other study found Vdss, VdB, and T1/2ß in uremics were reduced compared to normals.[2] Extrapolation of these data to diabetic patients with renal failure is complicated not only by the above inconsistent findings but also by the fact that diabetics may have altered hepatic clearance of drugs[3] and are frequently on multiple medications. Therefore, this study was undertaken to determine the pharmacokinetics of alfentanil in diabetic and non-diabetic patients undergoing renal transplantation.

Methods: After approval of the Committee on the Use of Human Subjects in Research and informed consent, six diabetic (Group I) and seven non-diabetic patients (Group II) undergoing renal transplantation were studied. Anesthesia was induced with thiopental 4-6 mg/kg and maintained with isoflurane at an end-tidal concentration of 0.3-0.8%. Ventilation was controlled to maintain end-tidal CO_2 between 30-38 mmHg. Forty minutes after induction of anesthesia 100 ug/kg of alfentanil was injected over one minute. Serial blood samples for alfentanil analysis were drawn over six hours from a central venous catheter and placed in heparinized tubes. Plasma was separated and frozen for subsequent analysis by radioimmunoassay. One, two, and three compartment models were fit to each patient's alfentanil plasma concentration-time data using weighted non-linear least squares regression. The Wilcoxon Rank Sum and Wilcoxon Signed Rank Tests were used to compare pharmacokinetic parameters between groups and within groups, respectively. A P value of less than 0.05 was considered significant.

Results: The plasma concentrations of alfentanil were most appropriately described by a two-compartment model in 11 of 13 patients. In the other two, a one-compartment model provided the best fit. Table 1 lists selected pharmacokinetic model parameters for each patient. They were calculated from data points obtained up to the time of renal revascularization. After revascularization the terminal T 1/2 increased from 0.96 ± 0.36 to 1.54 ± 0.56 hours in Group II ($p<0.05$). As shown in Table 1 the plasma clearance (CL) of alfentanil in the diabetic group (Group I) was significantly higher compared to the non-diabetic group, 6.36 ± 3.72 and 4.14 ± 1.02 ml/kg/min, respectively. Note that the two highest CL in Group I were 13.5 and 7.42 ml/kg/min (patients 5 and 1). In Group II the two highest CL were 6.15 and 4.87 ml/kg/min (patients 9 and 7) while the remaining five patients had CL less than 3.8 ml/kg/min. None of the patients in Group I had a CL below 4 ml/kg/min. Patient 5 with the highest alfentanil CL had had a pancreas transplant two years previously but still needed insulin supplementation and was receiving a number of medications including phenytoin and prednisone.

Discussion: The T1/2ß of alfentanil prior to perfusion of the transplanted kidney in Group II was identical to the 58 minutes reported by Van Peer et. al. in uremic patients. Their 58 minute half-life was significantly shorter than the 83 minutes they had determined in patients with normal renal function. Although the clearance of alfentanil was unchanged in patients with renal failure compared to normals in the two studies cited, it was significantly increased in our renal failure diabetic patients compared to the non-diabetic renal failure patients. Patient 5 contributed greatly to this difference with a clearance for alfentanil that was three times the mean of Group II. This latter observation suggests that the clearance of alfentanil, a drug with an intermediate hepatic extraction ratio, can be markedly increased in a diabetic on multiple medications that include hepatic enzyme inducers. The increase in the terminal T1/2 of alfentanil after renal revascularization indicates that the hemodynamic perturbations associated with the addition of a kidney to the central circulations can affect the pharmacokinetic disposition of alfentanil.

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Table 1: Alfentanil Pharmacokinetics in Patients Undergoing Renal Transplantation[*]

Patient number	Age (years)	Sex (M/F)	Weight (Kg)	VdB (L/kg)	$T_{1/2}B$ (hours)	CL (ml/kg/min)
Group I (Diabetics)						
1	30	M	75	0.61	0.96	7.42
2	35	F	71	0.36	1.0	4.15
3	47	M	86	0.34	0.91	4.29
4	49	M	73	0.33	0.82	4.70
5	33	M	78	0.54	0.46	13.5
6[b]	23	M	52	0.25	0.72	4.07
Mean±SD	36±10		75.5±11.3	0.41±0.14	0.81±0.19	6.36±3.72[*]
Group II (Non-diabetics)						
7	22	M	82	0.27	0.64	4.87
8	18	M	52	0.22	0.69	3.70
9	20	F	47	0.66	1.24	6.15
10	18	M	75	0.49	1.63	3.45
11	27	F	56	0.32	1.02	3.56
12[b]	19	M	72	0.21	0.73	3.37
13	46	M	72	0.26	0.79	3.8
Mean±SD	24±10.3		65±13	0.36±0.10	0.96±0.36	4.14±1.02
Combined Mean±SD	30±12		68±14	0.37±0.15	0.89±0.30	5.20±2.75

TITLE: THE EFFECTS OF GLOBAL NORMOTHERMIC HYPOPERFUSION ON PROCESSED EEG IN PATIENTS

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INTRODUCTION: Central nervous system morbidity remains as a major problem of general anesthesia. In an attempt to decrease morbidity monitoring by electroencephalography (EEG) in the operating room has been employed. Standard 16 lead electroencephalography is cumbersome and requires highly specialized training for its interpretation. To overcome these problems processed EEG's have been developed. The ability of processed EEG to detect perfusion deficits in animals has been reported, but similar studies on patients have been limited. Endocardial mapping and resection, and implantation of Automatic Implantable Cardioverter-Defibrillators (AICD) require the inducement of tachyarrythmias with resulting profound hypotension. This clinical scenario provides a unique clinical opportunity to examine the processed EEG. This study reports the effects of global normothermic hypoperfusion on the processed EEG during high-dose narcotic anesthesia.

METHODS: Eleven patients scheduled for AICD implantation, or myocardial mapping and resection were studied. Written informed consent was obtained from each patient and the protocol was approved by the institutional review board. Patients were evaluated preoperatively and a baseline neurologic exam was performed. Preoperative medication consisted of either morphine 0.1 mg/kg and scopolamine 0.005 mg/kg IM, or lorazepam 1-4mg PO one hour prior to arrival in the operating room. Cardiac medications were continued until the time of surgery. In addition to the standard monitoring, each patient had a radial arterial catheter and a pulmonary arterial catheter inserted. Anesthesia consisted of fentanyl (50-100 mcg/kg) or sufentanil (5-10 mcg/kg), midazolam 0.02-0.1 mg/kg), pancuronium (0.1 mg/kg), and 100% oxygen. After endotracheal intubation the patient's were ventilated to maintain normocarbia, and an esophageal temperature probe was inserted.

Each patient was monitored with a Nicolet Pathfinder I Compressed Spectral Array (CSA) quantitative EEG analysis system. Seven sterile subdermal needle electrodes were placed using the International 10-20 configuration: F_7, F_8, $C_3{}^1$, $C_4{}^1$, $T_1 1$, $T_1 2$, and a reference electrode at F_pz. This recording montage examines boundaries sensitive to ischemia in the sensory-motor strip fed by the middle cerebral artery, frontal lobe perfusion fed by the anterior cerebral artery, and occipital lobe perfusion fed by the posterior cerebral artery. The standard recording parameters were used: frequency bandpass = .25-16Hz, updated every four seconds, recording sensitivity 200 microvolts, filter bandpass =.5-30 Hz, spectral edge=98%.

During each period of cardiac stimulation the initiation and duration of profound hypotension was noted on the EEG recording for later analysis. The EEG's were graded as no change, transient change, and persistent change. A transient change was defined as a single four second global spectral edge reduction, and a persistent change was defined a global spectral edge reduction that persisted for more than one update period. Also both of these types of changes were associated with a loss of high frequency EEG activity.

RESULTS: In all eleven patients esophageal temperature remained above 36 degrees centigrade, and there were 110 intervals of sustained hypoperfusion secondary to ventricular tachyarrhythmias. These intervals ranged from 8 to 96 seconds and were accompanied by mean arterial pressures of 10 to 23 mmHg, and central venous pressures of 10-21 mmHg. Thus the cerebral perfusion pressure was almost 0. Four of the eleven patients showed no EEG changes despite 21 intervals of up to 24 seconds of hypoperfusion. The remaining seven patients had 89 intervals of hypoperfusion with 28 (25.5%) episodes of altered EEG recordings that included 9 (8.2%) transient and 19 (17.3%) persistent changes. These changes occurred as early as 4 seconds and as late as 68 seconds after the initiation of hypoperfusion. The incidence of EEG changes as a function of time of hypoperfusion is shown in the table. None of the patients devoloped neurologic complications postoperatively.

DISCUSSION: In this study of the effects of global normothermic hypoperfusion on the processed EEG two important observations emerge. First, in awake patients during electrophysiologic testing a much higher incidence of 16 lead EEG changes (68%) was noted only 10-15 seconds after the induction of ventricular tachyarrhythmias.[1] Either the processed EEG is not as sensitive in detecting global ischemia as the sixteen lead EEG, or the high-dose opiod anesthetic and 100% oxygen provides a masking or protective effect. Second, individual patients responded inconsistently to the hypoperfusion. For example in one patient, during one interval persistent changes in the EEG occurred as early as 16 seconds, but during a different interval no changes were seen after 36 seconds. Multiple factors can effect the processed EEG and further investigation is indicated.

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TABLE

Interval Duration or Time to EEG Change	<16 sec	16-25	36-35	>35
No. of Intervals	40	62	4	4
No. of Transient Changes	1	7	1	0
Percent	2.5%	11.3%	25%	0
No. of Persistent Changes	5	12	1	1
Percent	12.5%	19.4%	25%	25%

TITLE: TRANSESOPHAGEAL PULSED WAVE DOPPLER ECHOCARDIOGRAPHY AND THE HEMODYNAMIC RESPONSE TO VENTRICULAR PACING

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INTRODUCTION: In the normal heart, most ventricular filling occurs during the early rapid filling phase of diastole, and the remainder follows atrial systole. This biphasic filling pattern is reflected in transmitral velocity measurements obtained by transesophageal pulsed-wave Doppler echocardiography (PWDE). The aims of this study were to document mitral flow velocity patterns in anesthetized patients with ischemic heart disease and left ventricular dysfunction, and to investigate the relationship between transmitral velocity measurements and the hemodynamic response to ventricular pacing.

METHODS: Twenty-four patients in sinus rhythm without evidence of mitral valve disease undergoing elective myocardial revascularization were studied. Written informed consent was obtained from each patient and the protocol was approved by the Institutional Review Board. Anesthesia consisted of a high-dose opioid / muscle relaxant / oxygen technique. After tracheal intubation, a 3.5 MHz phased-array transesophageal echocardiographic probe was inserted and positioned to obtain a long-axis view of the left atrium(LA) and left ventricle(LV). The Doppler sample volume was placed at the mitral annulus with minimal cursor angulation, and the biphasic velocity tracing of transmitral blood flow was recorded. A hemodynamic profile consisting of measurements of heart rate (HR), mean arterial pressure (MAP), pulmonary artery diastolic pressure (PAD) was obtained and cardiac output was measured in triplicate by thermodilution. Asynchronous unipolar ventricular pacing was then instituted and following a one minute period of equilibration the hemodynamic and thermodilution measurements were repeated. Stroke index (SI), and cardiac index (CI) were computed using the standard formulae. The Doppler recordings were analyzed on a Dextra D-200 Cardiac Analyzer. The measured values included peak early filling velocity (E), peak atrial filling velocity (A), and the ratio of E:A. Based on the results of these measurements, the patients were divided into two groups. Those patients with an E:A above the median (0.88) were place into Group I (n=12), and those with an E:A below the median were placed into Group II (n=12). Intra-group comparisons were made using a paired Student's t-test to examine the effect of changing from SR to VP. Inter-group comparisons were made in SR and VP using an unpaired Student's t-test to examine the influence of E:A. Bonferroni's modification was applied to correct for multiple t-tests. Significance was defined as $P<0.05$. All data are reported as means ± standard deviation.

RESULTS: For the total population, E was 0.34±0.11 M/sec, and A was 0.38±0.09 M/sec. The mean E:A ratio was 0.91±0.30 and the median value was 0.88. In sinus rhythm, the CI of Group I was 1.97±0.32 l/min and Group II was 1.76±0.50 l/min (NS). SI of Group I was 37±7 ml/m^2 and 31±7 ml/m^2 for Group II (NS). During ventricular pacing, the patients in I (1.56±0.32 l/min) had significantly higher cardiac indices than those in II (1.21±0.31 l/min) ($P<0.02$). SI was also higher in I than II (24±6 vs. 19±4, $P<0.05$). There were no significant differences in HR, PAD and MAP. The E:A ratio correlated weakly ($r=-0.44$; $P<0.05$) with the percent change in stroke index.

DISCUSSION: In patients with a normal cardiovascular system, loss of atrial contraction results in minimal changes. However, in patients with cardiovascular disease, loss of atrial contraction may significantly reduce MAP, CI and SI. PWDE of transmitral blood flow provides a noninvasive method of examining left ventricular filling. This technique yields a recording of blood velocity over time through the mitral valve. In patients with synchronized atrial/ventricular contraction, the normal filling pattern is a biphasic tracing depicting a rapid early filling phase followed by diastasis, and completed with atrial contraction. In addition to peak velocity measurements, another easily-calculated parameter is (E:A). Based on the concept that peak E and A reflect the relative contribution of ventricular filling during their respective phases of diastole, this study examined the relationship between E:A and the hemodynamic response to loss of atrial contraction by asynchronous ventricular pacing. It was shown that these patients were significantly dependent on atrial contraction. Furthermore, in patients with E:A ratios below the median value, the hemodynamic response to ventricular pacing was more pronounced. These results are consistent with those of Pearson et al.[1] They showed that in awake patients the percentage increase in cardiac output obtained by optimization of atrial contraction weakly, but significantly correlated with Doppler derived E:A in an inverse fashion. In applying these conclusions there are two important factors to consider. Firstly, though the E:A ratio is an easily measured parameter of transmitral blood flow, it by no means is constant in a given patient. These filling velocities are effected by a multitude of factors which include the following: 1) LA compliance; 2) LA contractile state; 3) pulmonary venous return; 4) mitral valve function; 5) myocardial relaxation; 6) LA chamber stiffness; 7) external constraints (i.e., the pericardium); and 8) the phase of the respiratory cycle. Thus, in order for the assessment of atrial contraction to be valid, the determination should be made frequently and as close to the proposed intervention as possible. Secondly, patients in this study were separated into two groups with a dividing point of E:A = 0.88. This is a severely abnormal state and the results are only applicable to patients with severe cardiovascular disease. Since these are also the patients most likely to suffer from the loss of atrial contraction, the results of this study have clinical relevance.

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Title: ESWL DECREASES COMPLIANCE OF THE EPIDURAL SPACE BUT DOES NOT REDUCE THE EFFICACY OF REPEAT EPIDURAL ANESTHESIA

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Introduction:

Continuous lumbar epidural anesthesia offers significant advantages over spinal or general anesthesia in patients undergoing extracorporeal shock-wave lithotripsy for kidney stones. The reliability of repeated epidural anesthetics in this patient population has been questioned.[1] To assess whether repeat epidural anesthesia is associated with clinically significant problems related to changes in compliance of the epidural space, we measured epidural pressure in 30 consecutive patients requiring 2 sequential anesthetics for kidney ESWL.

Methods:

Unpremedicated sitting patients, received a lumbar epidural puncture (after giving their informed consent in accordance with requirements of the institutional human investigation committee) at L2, L3 or L4 using an 18 g Tuohy needle and air loss-of-resistance technique. Opening pressure (P_I) was measured with zero referenced to the hub of the needle using a standard pressure transducer.[2] Preservative-free lidocaine, 1.5%, was infused into the epidural space using an infusion pump (IVAC) set at 999 ml/hr. An initial 5 ml test dose and treatment dose to a total of 20 to 40 ml, predetermined by patient height and age, was administered. Epidural pressure measurements were repeated immediately after the test dose($P_{TEST\ 1}$), two minutes later($P_{TEST\ 2}$), immediately after the treatment dose($P_{FULL\ 1}$), and two minutes after the treatment dose($P_{FULL\ 2}$). An epidural catheter was then threaded 2-3 cm into the epidural space. Sensory levels to pinprick were obtained at regular intervals.

Patient age, height, weight, total dose of local anesthetic, initial sensory level, number of shocks given, and the interval between treatments were recorded. Identical doses were given for each treatment, and when possible, the second epidural was performed using the same interspace. Data from the first treatment (A) and second (B) were compared using ANOV.

Results:

There were no complications or failures of epidural anesthesia in any of the 30 patients following either treatment. There were no significant differences between treatments A and B for sensory level, P_I, $P_{TEST\ 1}$, $P_{TEST\ 2}$, or $P_{FULL\ 1}$ (Table). However, $P_{FULL\ 2}$ was significantly higher for treatment B ($p<0.05$). This difference was not associated with changes in the requirements for supplemental anesthesia, sedation or narcotic dose.

Discussion:

In conclusion, we found repeated epidural anesthetics for kidney ESWL to be safe, effective and reliable. However, our data support the theory that epidural anesthesia for ESWL is followed by changes in the compliance of the epidural space.

TABLE

	Treatment A	Treatment B
Level (T)	4.9 +/- 0.4	4.9 +/- 0.4
P_I (mmHg)	10.4 +/- 1.5	11.8 +/- 1.8
$P_{TEST\ 1}$ (mmHg)	28.7 +/- 1.9	31.1 +/- 1.6
$P_{TEST\ 2}$ (mmHg)	20.2 +/- 1.8	22.7 +/- 1.7
$P_{FULL\ 1}$ (mmHg)	46.9 +/- 2.5	52.5 +/- 2.7
$P_{FULL\ 2}$ (mmHg)	22.6 +/- 1.7	27.8 +/- 1.8*

* $p<0.05$

References:

1. Anesth Analg 66:669-72, 1987.
2. Anesth Analg 68:S288, 1989.

Title: WHAT ARE WE TRYING TO PROVE?

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Introduction:

We studied 49 consecutive patients scheduled for TURP or transurethral resection of bladder tumors, who consented to spinal anesthesia. The study was designed to determine whether 0.1 mg of morphine administered intrathecally provided adequate postoperative analgesia. Patients were warned of possible pruritus or nausea and were monitored by the nurses on the floor for delayed respiratory depression. All patients had an indwelling urinary catheter postoperatively. Pain relief was assessed subjectively (complaints of pain or bladder spasm) and objectively by recording the amount of analgesic (Tylox) taken during the first 24 postoperative hours. Approval of the institutional committee on human investigation was obtained. All patients gave consent prior to entry into the study.

Methods:

The first 19 patients received 0.1 mg morphine intrathecally and served as a pilot study. They were told they would receive morphine in their spinal to provide postoperative pain relief. The next 30 patients were identically treated except that they were randomized to receive either 0 mg, 0.1 mg, or 0.2 mg of morphine in their spinal and were told they might receive morphine intrathecally to alleviate postoperative pain.

Spinal anesthesia was performed in the sitting position at L3-4 with 100 mg of lidocaine in D.75 (2 ml). 0.5 ml (0.1 mg morphine in the pilot study) or 0.5 ml of study solution (0 mg,0.1 mg, 0.2 mg morphine) was added to the local anesthetic before injection. After 90 seconds, patients were placed in dorsal lithotomy position. Average spinal levels of T6 were obtained.

Results:

Patient characteristics were the same in both studies. All 19 patients in the pilot study reported satisfactory analgesia for the first 24 hours postoperatively. None required Tylox, nor did they experience pruritus, nausea, or delayed respiratory depression. In the study which followed only 50% of patients who received 0.1 mg morphine intrathecally experienced adequate pain relief (Table).

Discussion:

Results of analgesic trials are known to be dependent on adequate sample size and a randomized, prospective, double-blind study design.[1] In studies in which blindness is sacrificed to a detailed description of side-effects, therapeutic effectiveness of the study drug is enhanced,[2] probably due to "placebo".[3] Our study confirms the importance of the placebo effect in studies of post-operative analgesic regimens.

TABLE

	0 mg n-10	0.1 mg n-10	0.2 mg n-10	pilot study n-19
Tylox	2/10	5/10	0	0
Pruritus	0	3/10	4/10	0
Nausea	2	1/10	5/10	0
Resp.depress.	0	0	0	0

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Title:

THE EXPERIENCE OF THE PERSON VENTILATING THE LUNGS DOES INFLUENCE POSTOPERATIVE NAUSEA AND VOMITING

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Introduction. Postoperative nausea and vomiting continue to be common despite advances in the techniques used in general anesthesia. Factors stretching the stomach or gut wall may cause postoperative emesis by slowing down the motion of intestine or stimulating the emetic center directly. The aim of the present study was to find out whether the experience of the person performing mask ventilation in the beginning of anesthesia is related to the incidence or severity of emesis after the operation.

Methods. One hundred and ninety eight patients scheduled for abdominal hysterectomy were entered. The study protocol was accepted by institutional ethical committee and informed consent was obtained from each patient for the study. Only patients in ASA group I or II were entered. Patients were randomized according to rotating operating room schedules to be ventilated by an inexperienced person (anesthesiologists or nurses in training) or by an experienced person (staff anesthesiologists or experienced nurses). All patients were premedicated with meperidine 1 mg/kg i.m. Alcuronium chloride 1.5 mg, glycopyrrolate 0.2 mg and fentanyl 0.1 mg were administered i.v. two minutes prior to induction of anesthesia with 4 mg/kg of thiopental. Before tracheal intubation patients were ventilated trying to avoid the passage of gases into the stomach. Oral tracheal intubation was facilitated with 1.5 mg/kg of succinylcholine and anesthesia was maintained with isoflurane in combination with nitrous oxide and oxygen (30%). The inspired and expired concentrations of isoflurane were monitored with an anesthetic agent monitor. Patients were also given fentanyl as an adjunct in a standardized way (0.05 mg every 45 min). Alcuronium was used to maintain neuromuscular blockade; 20-25% of the patient's muscle power was maintained as assessed using a neurostimulator. End-tidal CO_2 was measured continuously with a capnometer and maintained at 5-5.5%. At the end of anesthesia, glyco- pyrrolate 0.4 mg and neostigmine 2.0 mg were given i.v. Oxycodone chloride was used to relieve postoperative pain. It was administered i.v. in the postanesthesia care unit in 4 mg increments and thereafter i.m. in the ward, at a dose of 0.13 mg/kg. The incidence of nausea and vomiting was determined at different intervals during the first 24 hours after the operation: from 0 to 2, 2 to 6, 6 to 12, 12 to 18 and 18 to 24 hours, as in our previous studies.[1,2] At the end of each interval a trained nurse, being unaware concerning details of ventilation registered whether nausea, retching or vomiting had occured. Droperidol 1.25 mg was administered once during each period for prolonged nausea or vomiting. Analysis of variance was used for comparisons of the patients' characteristics. The chi-square test was used to compare the incidence of emesis. The p-value less than 0.05 was considered statistically significant.

Results. Ventilation of the lungs was carried out in 124 and 74 patients by inexperienced and experienced persons, respectively. The two groups were similar in regard to age, weight, duration of anesthesia as well as in regard to history of nausea and vomiting after previous anesthesias and the drugs used during the present anesthesia (Table 1). Patients whose lungs had been ventilated by experienced persons had less emesis than patients whose lung were ventilated by inexperienced persons(Table 1). The amount of droperidol given for nausea and vomiting was significantly ($p<0.05$) higher in recovery room (0-2 hours postoperatively) in patients whose lungs were ventilated by inexperienced persons, when compared with patients ventilated by experienced persons.

Discussion. The trial design and scoring system used for nausea and vomiting in this study have been used by our group before and proved useful and sensitive in comparing anti-emetic drugs given before, during or after general anesthesia[1] and in studying the influence of nitrous oxide on postoperative emesis.[2] A comparison of emesis is justified in the present investigation, since the variables which most affect the incidence of nausea and vomiting (i.e. age, sex, type and duration of operation, amount of narcotics given) were similar in both groups. It is likely that an experienced member of anesthesia team was able to ventilate the lungs without pushing oxygen or gases into the stomach which might have attributed to postoperative nausea and vomiting. The difference between the groups was clear during the first two hours after operation and was still significant for as long as 6 hours postoperatively. In conclusion, the experience of the person ventilating the lungs may affect the outcome of early recovery period by reducing incidence of nausea and vomiting after general anesthesia in patients undergoing abdominal hysterectomy.

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Table 1. Groups and incidence of emesis

	Inexperienced Ventilation	Experienced Ventilation
No of patients	124	74
Age (yr)	43 ± 6	43 ± 4
Weight (kg)	64 ± 10	65 ± 10
Duration of Anesthesia(min)	95 ± 25	96 ± 32
Isoflurane conc. (Expired %)	0.9 ± 0.2	0.9 ± 0.2
Emesis:		
After 0-2 hrs	54%**	35%
Nausea	27%	27%
Retching	19%	7%
Vomiting	8%	1%
After 2-6 hrs	40%*	27%
0-24 hrs(overall)	79%	66%

* = P < 0.05 and ** = P < 0.01 vs experienced group

Title: ANTIEMETIC EFFICACY OF RANITIDINE, METOCLOPRAMIDE AND GASTRIC SUCTIONING IN OUTPATIENT LAPAROSCOPY

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Introduction:

In outpatient surgical facilities, postoperative nausea and vomiting remain the number one anesthesia-related side effect.[1] The incidence of postoperative nausea and vomiting have been reported as 36%-82%.[2] An effective prophylactic antiemetic regimen allowing optimum patient comfort and rendering the patient street ready in a short time would be significant. We routinely use both physical and chemical interventions to reduce the risk of aspiration in outpatients undergoing general anesthesia for laparoscopy. Unexpectedly, we observed a striking reduction in the incidence and severity of postoperative nausea and vomiting. We therefore examined, in a prospective study, the effects of ranitidine, metoclopramide, droperidol and gastric suctioning, in various combinations, on the incidence of nausea and vomiting in female outpatients undergoing laparoscopy under general anesthesia.

Methods:

Institutional approval and informed consent was obtained. Two hundred twenty-six adult female patients (17-35 years old, ASA I or II) undergoing outpatient diagnostic laparoscopy were studied. The control group had no intervention. Groups A, B, C, D, E and F received 150 mg of ranitidine and 10 mg metoclopramide orally the night before surgery. Group G received only 150 mg of ranitidine the night before surgery. The anesthesia regimen was standard for all patients. Each received 1 ug/kg of fentanyl intravenously (IV) followed by thiopental 3-4 mg/kg and succinylcholine 1.5 mg/kg IV to facilitate intubation. Anesthesia was maintained with isofluorane 0.75%-1.0% in 66% N_2O and 33% O_2. No other muscle relaxant nor narcotic was used. Patients were discharged following preset clinical criteria. Recovery room nurses noted the frequency of N & V by direct questioning and by telephone 24 hours after surgery. Group A patients received no other intraoperative treatment. Group B had gastric suctioning at the end of surgery. Group C patients received 20 ug/kg droperidol IV with induction. Group D received 20 ug/kg droperidol IV and gastric suctioning. Group E patients received IV metoclopramide 5 mg at induction and gastric suctioning. Group F patients received an additional dose of ranitidine (150 mg) three hours prior to surgery and gastric suctioning. Group G received only ranitidine 150 mg at bedtime and ranitidine 150 mg two to three hours prior to surgery and gastric suctioning. Chi square test was applied to find significant differences in incidence of N & V between groups.

Results:

Table 1 demonstrates the number (N) of patients in each group, mean time to discharge (Mean ± SEM in minutes) and incidence (%) of N & V. All treatments, except D, significantly shortened the mean discharge time from the control (ANOVA $p[<0.05]$). The incidence and severity of N & V was significantly reduced from control in groups B, E, F and G (Chi square $p[<0.05]$), whereas E, F and G were significantly different from B, but not one another.

Discussion:

This study demonstrates that emptying the stomach of its contents by physical and chemical means significantly reduces the incidence and severity of N & V postoperatively. The use of ranitidine, metoclopramide and gastric suctioning, in the various combinations tested, were equally effective and devoid of side effects. In addition, time to discharge was shortened. We conclude that these regimens provide a two-fold benefit: reduction of N & V and a reduction in the risk of aspiration.

TABLE 1

Group	(N)	RANGE (min.)	MEANS ± SEM	% N&V
Control	28	100-300	178.2 ± 8.4	45
A	20	120-195	156.3 ± 6.2	35
B	20	100-180	137.0 ± 6.0	20
C	20	110-300	179.2 ± 10.5	35
D	15	100-210	159.4 ± 7.8	27
E	54	110-225	155.6 ± 4.0	2
F	25	60-205	134.0 ± 7.9	4
G	44	90-120	139.5 ± 6.5	4

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Title:
EFFECTS OF BENZODIAZEPINES AND THE ANTAGONIST FLUMAZENIL ON OXIDATIVE MICROBICIDAL CAPACITY OF HUMAN NEUTROPHILS

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Introduction. Activated by soluble or particulate matter, neutrophil polymorphonuclear leukocytes (PMN) respond with a burst of oxidative metabolism, which is accompanied by chemiluminescence (CL). In recent years, the in vitro determination of the luminol-enhanced CL reaction has been used to study the effects of pharmacological agents on the oxidative microbicidal capacity of PMN (1). With the availability of the water-soluble short-acting benzodiazepine (BZD) midazolam and the specific antagonist flumazenil, BZD have been increasingly used for i.v. sedation. As we could recently demonstrate (2), a significant, dose-related depression of PMN migration occurred in the presence of diazepam and midazolam at concentrations exceeding 10^{-5}M (approx. 3 µg/ml). To date, only limited data exist on the influence of diazepam on CL (1), and nothing is known about the effects of midazolam, flunitrazepam and the new antagonist flumazenil on this PMN function.

Methods. After informed consent to participate in the institutionally approved study, purified PMN (>95%) were separated from the venous blood of 12 healthy volunteers (6 females, 6 males) by standard techniques as previously described (2,3). The donor group was restricted to 12 individuals in order to ensure that every compound was tested with the PMN of every donor. Viability was assessed by trypan blue dye exclusion in the presence and absence of BZD. Logarithmic dilutions (10^{-6}-5×10^{-4}M) of diazepam/Valium^R, flunitrazepam/Rohypnol^R, midazolam/Dormicum^R and the competitive antagonist flumazenil/Anexate^R were tested (kindly provided by <Roche>, Grenzach-Wyhlen, FRG). In order to detect any effects due to the solvents or other additives, the commercially available preparations as well as fresh solutions from the pure crystalline drugs and the drug-free original solvent mixtures were each examined in parallel runs. The luminol-enhanced CL response (1.5×10^6PMN/ml) to N-formylmethionyl-leucyl-phenylalanine (FLMP; 10^{-7}M) was measured in a six-channel Biolumat LB 9505 (Berthold, Wildbad, FRG) as already described (3). The medium control and five drug dilutions were always assayed simultaneously. The peak activity and the integral under the time-activity curve were expressed as a percentage of the donor's control response on that day. Differences in free radical scavenging, light absorption or interactions with the light enhancer luminol were investigated in a cell-free CL system containing luminol, horseradish peroxidase and hydrogen peroxide. Analysis of variance (ANOVA) was employed for comparison of treatments with the different compounds.

Results. At concentrations exceeding 10^{-5}M a significant ($P<0.001$), dose-dependent CL reduction was observed with all the BZD agonists tested (Fig.). However, at the lower, clinically relevant drug concentrations (10^{-6}-5×10^{-5}M, or approx. 0.3-15 µg/ml), their inhibitory potencies varied significantly ($P<0.001$; Fig.). Valium^R produced maximal inhibition (almost 50% depression at 10^{-6}M), followed by flunitrazepam/Rohypnol^R and midazolam/Dormicum^R, the latter showing no effect within the clinically relevant range. Parallel experiments with fresh solutions of pure crystalline diazepam revealed that the difference between Valium^R and flunitrazepam/Rohypnol^R was due exclusively to the solvent mixture used by the manufacturer (Fig.). As shown by the cell-free CL system, the effects of midazolam and flunitrazepam were caused by an interaction mainly with the cells, whereas Valium^R interfered considerably with other components of the CL reaction. The antagonist flumazenil/Anexate^R (10^{-7}- 5×10^{-5}M) had no significant influence on CL, and this was also true in the presence of stable inhibitory concentrations of midazolam.

Conclusions. The CL response measured in this study is closely linked to the oxidative microbicidal activity of PMN (4). At clinical concentration the extent of CL reduction varied widely with the BZD; in this respect, midazolam/Dormicum^R proved to be least suppressive, even at higher concentrations, whereas Valium^R produced maximal inhibition. Although this inhibition was caused partly by an interaction of the commercially used solvent mixture with extracellular components of the CL reaction, a suppressive effect on the patient's unspecific cellular immune response cannot be ruled out. Therefore, and for pharmacokinetic reasons, midazolam/Dormicum^R should be considered the most suitable BZD for high-dose long-term sedation. The BZD antagonist flumazenil, which by itself had no effect on CL, cannot antagonize the BZD-induced depression. Thus, no synergistic or antagonistic influence on the oxidative microbicidal capacity of PMN can be expected to result from the reversal of sedation by flumazenil.

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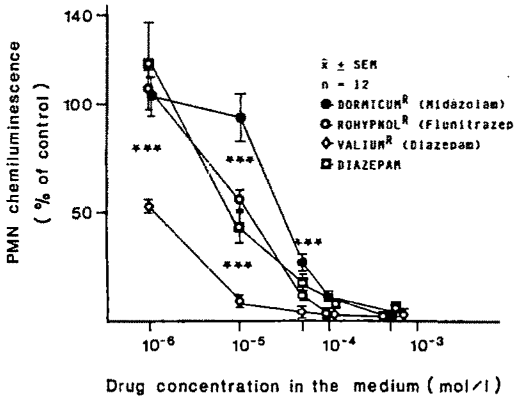
Figure.



Title : ALTERATIONS IN END TIDAL CO_2 DURING POSTOPERATIVE TRANSPORT

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Introduction. Several studies have reported arterial oxygen desaturation in patients during transport immediately following anesthesia and surgery (1,2). To date, however, no one has reported examining ventilation in this group of patients and its relationship to postoperatiave desaturation. Desaturation in the postoperative period may be the result of many physiologic alterations such as V/Q mismatch, diffusion hypoxia or inadequate respiratory drive. If depression of the respiratory drive occurs to a significant degree, then hypercarbia should also result. This study examined the degree to which hypercarbia accompanied hypoxemia in patients during the immediate postoperative period.

Methods. Forty-five consecutive ASA class I-III adult patients, free from any overt respiratory disease, undergoing elective upper and lower intraabdominal surgery were studied (approval received from the Institutional Review Board). Arterial oxygen saturation (SaO_2) was measured by pulse oximetery using the Nellcor N-100 pulse oximeter (Nellcor, Inc, Hayward, CA) preoperatively (room air), intraoperatively, prior to leaving the operating room ($FIO_2 = 1$), and immediately upon arrival in the Post Anesthesia Care Unit (PACU). In addition, end tidal concentrations of carbon dioxide ($ETCO_2$), anesthetic agent (ETAg), and nitrous oxide (ETN_20) were measured at those same times using an anesthesia circuit evaluator (Traverse Medical, Saline, MI). All patients received general endotracheal anesthesia. Details of all medications, including narcotics, muscle relaxants, and their reversal were recorded. No supplemental oxygen was given *en route* to the post anesthesia care unit (PACU). In the PACU, temperature, respiratory rate, and vital signs were recorded. The patients' level of conciousness was scored and recorded using a standard recovery scale (0= unresponsive, 1= arousable to calling, 2= awake). Supplemental oxygen ($FIO_2 = 0.35$) was then supplied to the patient via face mask.

Results. The mean age of the study group was 43 years (range 19-84 years). The mean surgical time was 142 min (mean) ± 64.9; S.D.), and mean anesthesia time 179 ± 78 min. The mean transport time between operating room and PACU was 8 ± 4.4 min. Mean temperature was 96 ± 1.2° F. The mean pre-induction room air saturation was 92.6 ± 2, mean final OR oxygen saturation at $FIO_2 = 1$ was 99 ± 1.46, and the mean SaO_2 upon arrival in the PACU was 92.6 ± 5.74, the difference between the final OR $Sa0_2$ and PACU $Sa0_2$ was significant, $p<0.0001$. Three patients exhibited severe hypoxemia to values less than 85 mmHg. There was a statisticaly significant drop in both mean ETAg, $p<0.0006$, and mean ETN_2O, $p<0.001$, during transport. Patients who had ETN_2O present prior to leaving the OR (mean 8.8%) had higher $ETCO_2$ levels upon reaching the PACU than did those patients with no ETN_2O present before leaving the O.R. ($p<0.019$), however, the change in $Sa0_2$ was not significant between groups. Elevations in CO_2 did not corelate with respiratory rate. There was no change in mean $ETCO_2$ between OR (42 ± 11 mmHg) and PACU (41 ± 8 mmHg). No statistically significant difference could be ascertained when comparing for change in $ETCO_2$ and level of conciousness, respiratory rate, smoking history, type of anesthetic, narcotics use or type and location of surgery.

Discussion. Many causes of postoperative hypoxemia have been proposed including inattention to patients, diffusion hypoxemia and a combination of nonspecific causes. Our data on $ETCO_2$ levels is important in that it allows us to further speculate and refine our thoughts on the etiology and physiology of postoperative hypoxemia. As statistically significant elevations of $ETCO_2$ were not found in spite of significant hypoxemia, by definition hypoventilation may be effectively ruled out as an etiology. In addition, the mean respiratory rate was 18 (range 8-28) breaths per minute (volumes were not measured). Diffusion hypoxemia is also an unlikely cause because the time course of this is on the order of 2.5 min (3). Our data also show that desaturation occurred in patients who had no detectable ETN_2O prior to transport from the OR. All postoperative desaturation in our study was O_2 responsive and, therefore, by definition, shunt ($V/Q = 0$) can also be ruled out as a cause. Oxygen responsiveness is also consistent with the most common cause of hypoxemia, that is, V/Q mismatch (4). Even though patients in our study demonstrated oxygen desaturation in the immediate postanesthesia period, $C0_2$ retention was not significant, therefore, supplemental oxygen can be safely administered without masking hypoventilation.

Conclusion. Postoperative hypoxemia, which occurs during transport between the OR and the PACU, is most likely caused by increased V/Q mismatch. Retention of CO_2 during transport did not occur in patients with previously normal lung function anesthetized at our institution. Many patients may benefit from supplemental oxygen during postoperative transport between the OR and PACU.

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Title: TOXIC PROFILES OF BUPIVACAINE IN YOUNG PIGS RECEIVING DIFFERENT INHALATION ANESTHETICS

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Introduction. Although regional anesthesia may be used as the sole technique in infants and children, most anesthesiologists use regional anesthesia as an adjunct to general anesthesia with an inhalation agent.[1] It is unknown whether the toxic profile of local anesthetics is the same regardless of which inhalation agent is used. Therefore, we studied the effects of different inhalation anesthetics on the toxicity of bupivacaine.

Methods. After approval from the Animal Care and Use Committee, we studied 30 farm bred pigs aged two-days. Based on their ages at onset of puberty a two-day-old pig would be analogous to a six-week-old infant. In all pigs, anesthesia was induced using halothane or isoflurane, with or without 70% N_2O. After tracheal intubation, ventilation was controlled with a Siemens-Elema 900D Ventilator. Arterial PCO_2 was maintained at 32-36 mmHg. The electrocardiogram (ECG) and fronto-occipital electroencephalogram (EEG) were continuously recorded.

Catheters were inserted into 1) femoral artery for continuous blood pressure measurement, 2) inferior vena cava (via the femoral vein) for drug and fluid administration and, 3) contralateral femoral vein for blood sampling. After muscle relaxation with pancuronium the pigs (6 in each group) were allowed to stabilize for 30 minutes on 70% N_2O/30% O_2 without volatile anesthetics (N), 0.5% halothane/70% N_2O)/30% O_2 (H+N), 0.94% halothane/100% O_2 (H), 0.77% isoflurane/70% N_2O/30% O_2 (I+N) or 1.54% isoflurane/100% O_2 (I) and given D_5LR (25 ml/kg) intravenously.

Bupivacaine was then continuously infused at 1 mg/kg/min using an infusion pump. The threshold doses of bupivacaine were recorded for each of four events: 1) first ventricular dysrhythmia (DYS), 2) first seizure (SZ), 3) isoelectric EEG (ISO EEG), and 4) asystole (ASYS). Every five minutes during the infusion, cardiac output was determined non-invasively[2] and blood was sampled, separated, and frozen at -80°C for measurement of plasma concentrations of bupivacaine by HPLC. Differences among the groups for plasma concentrations and threshold doses of bupivacaine were compared using one-way ANOVA and the Student-Newman-Keuls test.

Results. Bupivacaine plasma levels at all sample times were equal in all groups. In all animals of the N_2O + O_2 group, the first toxic sign was cardiac dysrhythmias followed by seizures, isoelectric EEG, hypotension, then asystole.

The appearance of toxic signs was different in animals in the other groups (Figure). No seizures were seen in any of the pigs receiving halothane. In the 0.5 MAC isoflurane +70% N_2O group only one pig of six had dysrhythmias and two had seizures. In the 1 MAC isoflurane +100% O_2 group, two pigs had dysrhythmias and only one had seizures. Cardiac output was best maintained in the N group, and second best in the I+N group.

Discussion. It is clinically useful to be able to observe the early warning signs of central nervous system and cardiac toxic responses to local anesthetics. In our study, seizures were prevented by halothane and attenuated by isoflurane. Dysrhythmias were not consistently observed with isoflurane or 1 MAC of halothane. These data suggest that the margin of safety between the onset of dysrhythmias (when they occur) and life threatening cardiovascular depression may be narrow in infants given bupivacaine during N_2O plus either halothane or isoflurane anesthesia.

Our pigs had controlled ventilation and were normocarbic. Bupivacaine toxicity may occur earlier in children if they become hypercarbic during anesthesia with a volatile agent. Since dysrhythmias occur most frequently in infants and children during the induction of anesthesia, a failed regional technique using bupivacaine followed by the induction of anesthesia with N_2O and halothane may impose additional risk of cardiotoxicity.

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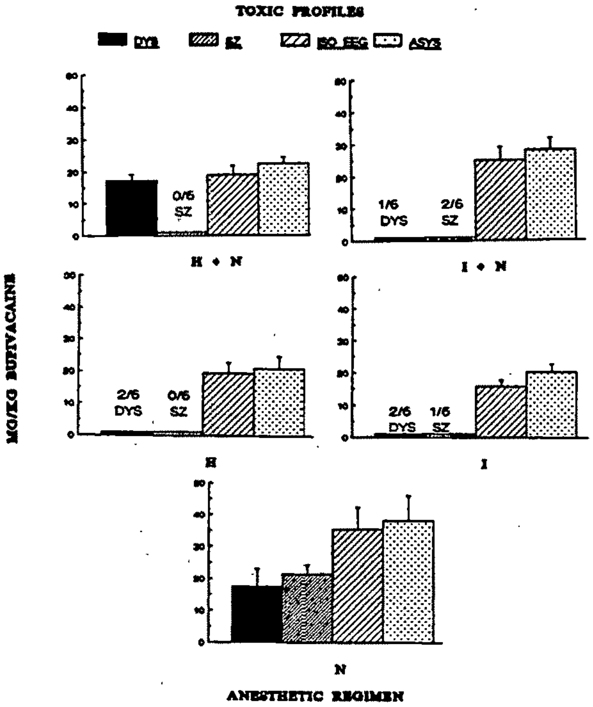

TITLE: ACETYLCHOLINE RECEPTORS AND RESISTANCE TO ATRACURIUM IN HUMANS WITH THERMAL INJURY

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INTRODUCTION: Thermal injury has been associated with resistance to non-depolarizing neuromuscular blockers[1]. Pharmacokinetic studies have been unable to account for burn related d-tubocurarine hyposensitivity. It has been suggested through animal studies that there is an increase in the number of skeletal muscle acetyclcholine (ACh) receptors[2], and that these additional receptors are somehow responsible for resistance to non-depolarizing muscle relaxants. Here, we document the increase in number of ACh receptors found in skeletal muscle of humans with thermal injury, and attempt to correlate this finding with clinical resistance to atracurium.

METHODS: This project was approved by the Committee on Research Involving Human Subjects for the State University of New York at Stony Brook and written informed consent was obtained from each patient participating in the study. Twenty-three patients with thermal injury and fifteen control patients were studied at the time of elective surgery. General anesthesia was induced with thiopental (4 mg/kg iv) and a mask airway was established for administration of oxygen (40%), nitrous oxide (60%), and isoflurane (0-0.6%). Neuromuscular transmission was monitored by administering trains-of-four transcutaneous stimuli (0.5Hz along the ulnar nerve every 20 seconds and recording the amplitude of the resulting compound action potential from the thenar musculature. After measurement of the control response to ulnar nerve stimulation, atracurium (0.4 mg/kg iv) was given. The onset of neuromuscular blockade was recorded as the time, in minutes, between the initial bolus of atracurium and a decline in amplitude of the compound action potential in response to the initial twitch in a train-of-four stimuli (T_1) to 50% of the control response. Tracheal intubation was performed when T_1 reached 5% of the control response. Anesthesia was maintained with sufentanil (0.5-1.0 ug/kg/hr iv), and intermittent doses of atracurium (0.5mg/kg iv) were given each time T_1 returned to 10% of the control response. Isoflurane was discontinued or reduced after the induction of anesthesia. Mechanical ventilation was instituted to maintain an end-tidal pCO_2 between 35 and 40 mmHg throughout the procedure. During the course of the operation, two small specimens (approximately 0.5 mg) of viable skeletal muscle were taken from the surgical field so that ACh receptors could be quantified by means of an I^{125}-labelled α-bungarotoxin binding assay.

RESULTS: Sensitivity to atracurium was measured as a function of the onset of neuromuscular blockade and atracurium requirement. Onset of neuromuscular blockade was recorded as the time, in minutes, between the initial bolus of atracurium and a decline in T_1 to 50% of the control value. Atracurium requirement was recorded as the maintenance dose requirement (MDR) and the maintenance dosing interval (MDI). MDR is the total amount of atracurium given as a maintenance dose per body weight per unit time (ug/kg/min). MDI is the time (minutes) between the required maintenance doses. Both the onset of neuromuscular blockade and the atracurium requirement as determined by MDR and MDI were significantly different ($p < 0.02$) as shown in Table I. The mean ACh receptor concentration was also significantly higher for the group ($p < 0.02$) as shown in Table II. Figure 1 shows that for all patients, there is no correlation between ACh receptor concentration and onset of neuromuscular blockade. This study also demonstrated the lack of a correlation between ACh receptor concentration and atracurium requirement (MDR or MDI). Similar results were obtained when examining the ACh receptor concentration and sensitivity to atracurium in the burn group alone.

DISCUSSION: This is the first quantitative study in humans to show that thermal injury is associated with an increase in nicotinic ACh receptor concentration in skeletal muscle. In agreement with Dwersteg, this study also demonstrates that burn patients are resistant to atracurium. The mechanism by which thermal injury induces resistance to non-depolarizing neuromuscular blockers remains unknown. Proposed mechanisms include an increase in junctional ACh receptors which would increase the amount of non-depolarizing neuromuscular blocker necessary to affectively compete with acetylcholine. If this is true, one would expect to see an increase in the onset of time and maintenance atracurium requirements as we have shown in our study. This decrease in sensitivity to atracurium, however, should correlate with the concentration of ACh receptors. Clearly, in our study, there is no correlation between ACh receptor concentration and onset of neuromuscular blockade or maintenance atracurium requirement. Another proposed mechanism is that the increase in ACh receptors is primarily extrajunctional. These extrajunctional receptors might bind non-depolarizing neuromuscular blockers, thus making less drug available to compete with acetylcholine at the junctional receptor sites. If this mechanism were at work, maintenance dose requirement may or may not change depending on the degree of saturation of the extrajunctional receptors, but one would still expect to see an increase in onset time that correlates with ACh receptor concentration. These conditions do not hold true for our study. Thus, although the method used does not distinguish between junctional or extrajunctional ACh receptors, neither of these alternative can plausibly account for resistance to atracurium in whole.

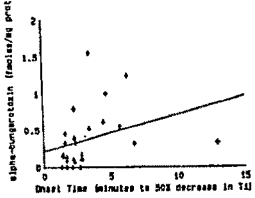
Table I Sensitivity to Atracurium

	Control Group	Burn Group	p Value
Onset(min)	2.19±.856(15)	4.33±3.13(13)	p 0.02
MDR(ug/kg/min)	6.3±1.91(11)	11.5±4.27(10)	p 0.01
MDI (min)	17.2±4.19(11)	9.24±2.91(10)	p 0.01

Table II Nicotine ACh Receptor Concentration

	Control Group	Burn Group	p Value
x-bungarotoxin binding (fmoles/mg protein)	.242±0.247(15)	0.519±0.385(23)	p 0.02

Figure 1.



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CEREBRAL BLOOD FLOW AUTOREGULATION DURING ADENOSINE-INDUCED HYPOTENSION IN DOGS

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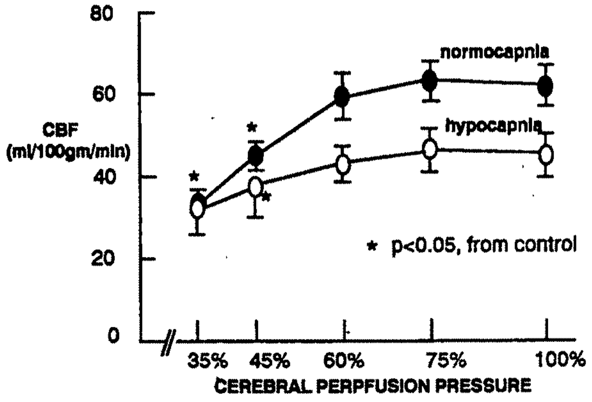
Introduction: Adenosine is the purported metabolic mediator of cerebral blood flow(CBF) autoregulation.[1] Although it has been used clinically as a hypotensive agent in limited studies, the influence of adenosine on CBF has been inconsistent in experimental investigations.[2] Moreover, autoregulation during adenosine-induced hypotension with step-wise change in cerebral perfusion pressure(CPP) has not been studied. Accordingly we evaluated the influence of adenosine on CBF during graded decrease in CPP in dogs during both normocapnic and hypocapnic conditions.

Methods: The study was approved by the institutional animal care committee. Six mongrel dogs, weighing 15 to 20 kg, were anesthetized with halothane. Following tracheal intubation, anesthesia was maintained with halothane 0.6% inspired, nitrous oxide 70% and a continuous infusion of pancuronium. Catheters were inserted into the femoral artery for direct BP measurement, into the sagittal sinus for measurement of CBF using the venous outflow technique, and the ventricular cistern for measurement of intracranial pressure(ICP). Step-wise decrease in CPP(100%,75%,60%,45%,and 35%) was induced with adenosine(5.3mg/ml) infusion. Each CPP step was maintained for at least 10 minutes before collection of data. The following variables were recorded at each step: (1) CPP (2) ICP (3) cerebral metabolic rate($CMRO_2$) (4) CBF in triplicate and(5) bilateral EEG recorded with a Lifescan monitor (Diatek,California). % CPP was always calculated according to the baseline CPP recorded during normotension in the beginning of the experiment. In each dog both normocapnia(pCO_2=40 mmHg) and hypocapnia(PCO_2=20 mmHg) were studied, with the study sequence randomized. At least one hour was allowed to lapse after the initial study before the next experimental series was begun. For each CO_2 level, the data were analysed with ANOVA for repeated measures and Fisher's PLSD. Comparison between normocapnia and hypocapnia was assessed with two-way ANOVA. A p value of less than 0.05 was considered significant.

Results: Hypotension was easily induced with adenosine. There was no difference in systemic blood pressure or CPP between the two experimental conditions at each step. Control CBF during hypocapnia was approximately 25% less compared to CBF during normocapnia. With step-wise decrease in CPP, CBF was unchanged from normotensive values during both normocapnia and hypocapnia until CPP reached 60% of control, and thereafter declined in a linear fashion with CPP. (Figure). The decline was steeper during normocapnia than during hypocapnia and when CPP was35% of control CBF was identical in both groups. CBF during 45% and 35% CPP was significantly less than control values in both groups. EEG was unchanged until CPP decreased to 35% , when th % delta activity in the total EEG power increased significantly and the corresponding % beta activity decreased in both groups. $CMRO_2$, however, was unchanged throughout during the study during both normocapnia and hypocapnia.(TABLE)



%CPP		control	75%	60%	45%	35%
actual CPP	Ncapnia	81±6	62±4	50±4	37±3	29±3
mmHg±sem	Hcapnia	89±6	63±4	47±3	37±3	29±6
$CMRO_2$	Ncapnia	3.74±.75	4.38±.81	4.20±.67	4.18±.45	3.32±.32
ml/min/100g	Hcapnia	3.77±.73	4.03±.49	4.18±.48	4.35±.56	3.68±.45

Discussion: Newberg[3] had previously demonstrated that CBF decreased by 54-65% when BP was reduced to 50 and 40 mmHg (CPP of 31-33 mmHg and 22-24 mmHg). However, the influence of adenosine on autoregulation was not studied. Our study demonstrated that CBF was maintained until CPP fell to 45% of control, corresponding to 37 mmHg. The maintenance of normal $CMRO_2$ was consistent with their findings. In this study we have delineated the influence of pCO_2 and found that the lower limit of autoregulation was not affected by hypocapnia, and that the CO_2 reactivity was preserved until this lower limit was reached, after which CBF declined towards the same value regardless of the level of CO_2. Although our results indicated that autoregulation remained intact until CPP decreased to about 37 mmHg, the slight increase in CBF during the first step decrease in CPP suggested that the apparent maintenance of CBF could also be explained by a balance between the vasodilating action of adenosine and a declining perfusion pressure. This explanation, however, seems unlikely since adenosine does not cross the blood brain barrier. We conclude that CBF autoregulation is intact during adenosine-induced hypotension and that adenosine may be employed safely as a hypotensive agent provided that the lower limit of autoregulation is not exceeded.

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Title: Measurement of Cardiac Output By Transesophageal Pulsed Wave Doppler: Comparison of Two Techniques

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The transesophageal window for pulse wave Doppler (PW) provides a convenient site for signal acquisition during general endotracheal anesthesia. Prior attempts to measure cardiac output by techniques applicable to intraoperative patient care have lacked sufficient accuracy to be clinically useful.[1] Utilizing 2D-images and PW by the transesophageal echo(TEE) approach two practical methods for the intraoperative measurement of cardiac output are examined.

METHODS. TEE 2D- and PW signals were obtained from 12 patients undergoing coronary revascularization without significant valvular disease using an HIC approved protocol. A 5.0 MHz TEE probe (Hewlett Packard 77020) was positioned in the esophagus to obtain Transmitral flow signals at both the mitral valve annulus and leaflet tips and recorded on VHS videotape. 2D images (5 chamber view) of the mitral valve were obtained from the same transducer position to measure mitral annulus diameter and leaflet separation. Thermodilution cardiac output (TDCO) measurements were obtained in triplicate during end-expiration with room temperature injectate. Doppler stroke volume was calculated by integrating the flow velocity waveform and multiplying by the cross-sectional area of flow at the site of measurement. Conversion to Doppler cardiac output (DCO) was achieved by multiplying heart rate x stroke volume. DCO was computed using mitral annulus data (DCO_A) and mitral leaflet tip data (DCO_L) and compared to TDCO. Each DCO represents the average of three consecutive stroke volumes multiplied by heart rate. Finally the average for the two Doppler cardiac output methods was compared to TDCO. Data was analyzed by linear regression and calculation of correlation coefficients (r).

RESULTS. (Table 1 and Figure 1) Comparison of the data for DCO and TDCO revealed that DCO_L correlated best with TDCO with a mean error of 13%. Averaging the results of the two Doppler techniques did not improve correlations with TDCO.

DISCUSSION. We have compared two techniques to measure cardiac output by transesophageal PW Doppler to TDCO. Measurement of Doppler cardiac output at the mitral leaflet tips strongly correlates with TDCO. Choice of a single imaging plane in obtaining both the Doppler data and the 2D measurement of diameter is of practical importance as it can be performed during the intraoperative period. A prior study by Meijboom et al demonstrated that this approach utilizing transthoracic Doppler in children was accurate.[2] The measurement of the diameter of the leaflet tip orifice at end-diastole further simplifies the approach as current TEE units allow for the ECG gated acquisition of 2D images. The clinician does not need to review multiple video frames to find the appropriate time to complete the diameter measurement. Comparison of mitral leaflet with mitral annulus measurements revealed that the later site was not as accurate and tended to overestimate CO. Combining the DCO measurements from both sites did not increase the correlation with TDCO in comparison to mitral leaflet measurements (r=.67 vs r=.80) TEE measurements of CO are attractive because 1) the noninvasiveness of the technique 2) the flat flow profile at the mitral valve 3) the small angle between the ultrasonic beam and the direction of blood flow 4) the proximity of the probe tip to measurement site. The present study demonstrates that Doppler measurement of cardiac output at the mitral leaflet tips gives good estimates of CO compared to TD by a method that can be performed in the operating room.

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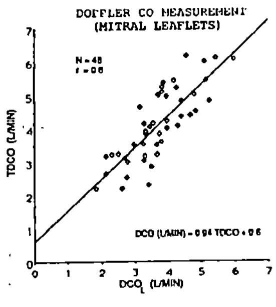
TABLE I
n=48

	r	slope	SEE
DCO_L	.80	.94	.64
DCO_A	.65	.67	.81
Combined	.67	.90	.69



Title: DROPERIDOL -PRETREATMENT AND *IN VITRO* EFFECTS ON RAT SKELETAL MUSCLE CONTRACTURE

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Introduction:

In vitro muscle preparations are well established models used to screen for the malignant hyperthermia (MH)-inducing properties of anesthetic agents. Droperidol (DPD), a potent neuroleptic drug, is widely used in general anesthesia and neurolept analgesia. Results from *in vitro* pharmacological studies (1) in which DPD was used at a concentration of 10 μM suggest that DPD may be considered as a safe anesthetic adjunct for use with MH-susceptible individuals. In the present study, the effects of *in vivo* pretreatment with DPD on skeletal muscle contractures induced *in vitro* by succinylcholine and halothane as well as the effects of different concentrations of DPD administered *in vitro* were examined.

Methods:

After obtaining approval from the institution's animal review committee, male Sprague-Dawley rats (250-300 g) were used for this study. The diaphragm was removed and placed in Krebs solution (pH 7.4) bubbled with oxygen and carbon dioxide (95:5). Strips of diaphragm were prepared and mounted in Krebs in a tissue bath at 37° with oxygen and carbon dioxide (95:5) and directly stimulated at 0.2 Hz. A stable resting tension of 1 g was maintained for 30 minutes. Subsequently, succinylcholine at a final concentration of 50 mM was added to the muscle bath for 5 minutes. Halothane (1%) was then vaporized into the gas phase for 5 minutes followed by a final exposure to 3% halothane for 5 minutes. Those animals that were pretreated with DPD (0.35, 0.70, 1.40 or 2.80 mgs/kg) were injected one hour prior to sacrifice. When DPD (10, 25, 50, or 100 μM) was given *in vitro*, it was added 5 minutes prior to the addition of succinylcholine. Maximum contracture values were recorded and analyzed using one-way analysis of variance. Values were considered significant at $p<0.05$.

Results:

Mean maximum contracture tensions for each dose of DPD for each condition are shown in the tables. For both control and when DPD was either used as a pretreatment or given *in vitro*, there were progressive increases in tension when the muscle was exposed to succinylcholine (sux) followed by halothane (1% and 3%). At all doses of DPD, when given as a pretreatment, contracture tensions for all triggering conditions were significantly reduced from that of control conditions. When given *in vitro*, DPD had a significant effect on contractures induced by succinylcholine but not on halothane-induced contractures in preparations pre-exposed to succinylcholine.

Discussion:

While a number of factors may trigger MH, the defective regulation of myoplasmic calcium concentrations is believed to be the primary mechanism that initiates MH. Pretreatment with DPD one hour prior to *in vitro* testing significantly reduced muscle contractures produced by known triggering agents. However, when DPD was given *in vitro*, irrespective of the concentration, only succinylcholine-induced contractures were significantly affected. The observed differences between the *in vivo* and *in vitro* treatment may be due to complex interactions or different loci of action *in vivo*. Results of the present investigation support evidence from previous studies that suggests that DPD may be considered as a safe adjunct to anesthesia for MH-susceptible individuals.

References:

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In Vivo DPD DOSE (mgs/kg)	N	MEAN CONTRACTURE (g) AFTER *IN VITRO* TREATMENT WITH Sux*	1% Hal*	3%Hal*
0	12	0.21	0.47	0.64
0.35	5	0.11	0.29	0.43
0.70	5	0.12	0.39	0.51
1.40	5	0.15	0.30	0.53
2.80	5	0.18	0.44	0.62

In Vitro DPD DOSE (μM)	N	Sux*	1% Hal	3% Hal
0	12	0.21	0.47	0.64
10	4	0.15	0.52	0.69
25	4	0.16	0.42	0.55
50	6	0.19	0.50	0.61
100	6	0.30	0.58	0.71

* Significant differences within these groups ($p<0.05$).

TITLE: RAPID CHANGES IN AUTONOMIC REFLEXES INDUCED BY PENTOTHAL: ASSESSMENT BY A NEW METHOD

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INTRODUCTION: Power spectral analysis of heart-rate variability (HRV) has been validated as a noninvasive technique for the study of autonomic nervous system (ANS) function.[1,2] These HRV power measurements quantify the frequency and amplitude of small variations in heart-rate (HR) caused by homeostatic ANS reflexes. HRV power above 0.125 Hz (P_H) correlates with parasympathetic (PS) activity, while HRV power below 0.125 Hz (P_L) is influenced by both sympathetic (SY) and PS activity. Induced changes in SY and PS activity (e.g., by tilting the patient or infusing neosynephrine) cause corresponding changes in P_L and P_H.

Prior studies have limited analysis to long periods (typically 256 sec) of steady-state HR data. We investigated the use of digital preprocessing techniques, followed by analysis of shorter data windows (64 sec), to evaluate more rapid changes in ANS function. This abstract briefly describes this technique, and presents some graphs of results derived from data taken during induction of anesthesia with pentothal (P).

METHODS: This study was approved by our Institutional Review Board, and informed consent was obtained from all patients. Subjects were 9 ASA class I elective surgical patients aged 18 to 35. After premedication with 0.15mcg/kg sufentanil IV, patients were induced with 4mg/kg P IV given over 10 seconds. Patients were then paralyzed with vecuronium and ventilated with 100% O_2 (n=4) or 60% N_2O (n=5) for the three minute study period.

EKG data for HRV analysis were obtained using a microcomputer with an A/D converter sampling at 250 Hz. The digitized EKG was first converted to an instantaneous HR signal; this signal was subjected to digital bandpass filtering which removed components below 0.0312 Hz and above 0.5 Hz. This filtering process removed frequency components which could not be accurately assessed by our subsequent 64 sec FFT algorithm for power spectral analysis.

The ability of our analytical approach to follow rapid changes in the spectral components of HRV was validated with simulated ECG data generated by a computer program.[3].

RESULTS: Directional changes in SY and PS activity, as suggested by changes in P_L and P_H, were found to correlate with the observed changes in mean HR caused by P (figures 1 and 2). Both the HRV power spectral surface and the original HR signal from which this surface was derived are depicted. The lines making up the spectral surface (spaced 15 seconds apart) represent the power spectra derived from overlapping 64 sec data windows of the HR signal centered about the location of the respective spectral line on the time axis.

The time at which P was injected is denoted by "P" in each figure. Note that P injection in patient 1 (fig. 1) resulted in significant tachycardia. This increase in HR coincided with a rapid decrease in P_H (indicating a decrease in PS activity) and an initial increase in P_L (increase in SY activity). HR then decreased as P_L (SY activity) decreased. This is the most common pattern of changes in HRV power which we have observed (regardless of whether patients were ventilated with 100% O_2 or 60% N_2O).

Figure 1

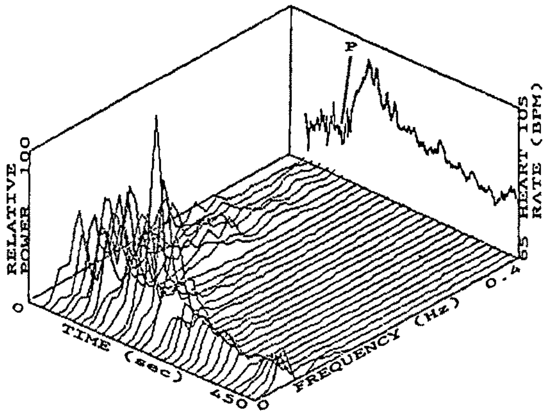
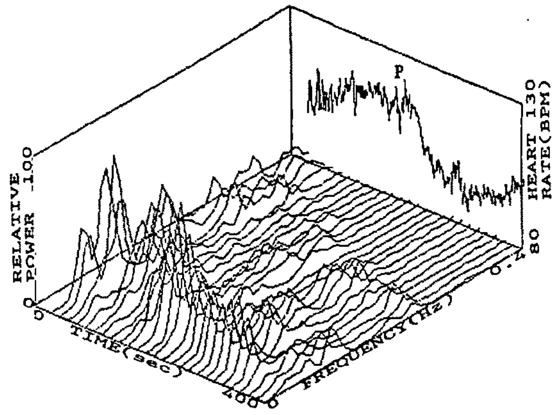


Figure 2



The HR response to P injection in patient 2 is shown in figure 2. This patient became very anxious a few minutes prior to induction, and exhibited an increase in HR, an increase in P_L, and a decrease in P_H with this anxiety. Subsequent P injection had less effect on the remaining P_H, but led to a dramatic decrease in P_L. This patient did not exhibit an initial increase in HR, consistent with the lesser effect of P on P_H (PS activity) and the lack of initial increase in P_L (SY activity). The subsequent decrease in P_L (SY activity) was accompanied by a corresponding decrease in HR.

DISCUSSION: These initial results suggest that sequential spectral analysis of the prefiltered HR signal may allow assessment of rapid changes in ANS function. As such, this technique may be a valuable noninvasive tool for the study of ANS function in anesthetized man.

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EFFECTS OF MIDAZOLAM ON MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS DURING LUMBAR SPINE SURGERY

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Introduction This study evaluates the effects of a bolus of Midazolam in 10 patients on median nerve somatosensory evoked potentials (SSEP) undergoing lumbar spine surgery.

Methods All patients, after giving informed consent, received 0.06 mg/kg of Midazolam i.m. 1 1/2 hours before induction of anesthesia. Induction of anesthesia was achieved with Midazolam 0.2-0.3 mg/kg i.v. with muscle relaxants for intubation. SSEP were measured preoperatively the night before surgery, 1 hour after premedication with Midazolam, and after induction with Midazolam for 1 hour (1,5,10,15,30,60 mins. after injection of Midazolam). The median nerve was stimulated at motor threshold or up to 150% of threshold to optimize the response. The SSEP were recorded at sensory cortex on the contralateral and ipsilateral side. Recordings were done with a CTC 2050 Evoked Potential Monitor (Clinical Technology Corporation).[1] In all patients, Midazolam was the sole anesthetic agent given until at least 10 minutes after induction.

Results The results show a significant decrease in amplitude from 5 minutes after Midazolam injection that persisted for 60 minutes. There was a significant increase in latency from 10 minutes postinjection as well, that persisted through the 60 minutes of the study (results were analyzed by a Dunnetts T-test).[2]

Discussion For clinical purposes, an increase in latency of 50% and a decrease in amplitude of 50% are considered significant. There was a decrease in amplitude that was clinically relevant, however, the latency was maintained. When using evoked potentials, this effect of Midazolam must be taken into consideration if it is used in induction doses. The premedicant dosages didn't demonstrate any change in the evoked potential response however.

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	LATENCY			AMPLITUDE		
Time	Mean (mS)	St. Dev. (mS)	Dunnett t	Mean (mV)	St. Dev. (mV)	Dunnett t
Preop	18.58	1.05		3.14	0.98	
1 min	19.00	0.75	1.22	2.52	1.15	3.17
5 min	19.50	1.06	2.68	2.00	0.99	5.86 *
10 min	19.99	1.10	3.98 *			
15 min	20.21	1.09	4.22 *	1.55	0.88	8.21 *
30 min	20.25	1.45	4.87 *	1.18	0.62	10.09 *
60 min	20.19	1.71	4.71 *	1.07	0.64	10.67 *

* Significant at 95%

Title: DOES A CONTINUOUS INFUSION OF INTERPLEURAL BUPIVACAINE OPTIMIZE POST CHOLECYSTECTOMY PAIN RELIEF?

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INTRODUCTION: Several studies have reported good pain relief post cholecystectomy with bolus injections of bupivacaine (BUP) through an interpleural catheter (IPC)[1,2,5]. Commonly in these reports, the catheter is placed at the conclusion of the operation; local anesthetic is injected; and the patient awakened. The catheter is re-injected with local anesthetic as needed to maintain adequate analgesia. The interval varies among patients and can be as frequent as every four hours [2,3]. This method of pain relief is extremely labor intensive to members of a department of anesthesia. A previous study has quantified the decreased need for parenteral narcotics compared to that of patients not receiving interpleural analgesia [4,5]. However, no study has contrasted the efficacy and safety of continuous infusion versus bolus injections of anesthetic in providing pain relief.

METHODS: Following approval of our Institutional Review Board, 17 ASA I & II patients for cholecystectomy agreed to participate in the study. All patients underwent general anesthesia with an inhalation agent and received 100 mcg of Fentanyl towards the conclusion of the operation. The effects of muscle relaxation were reversed and the patient was allowed to breathe spontaneously while the IPC was placed. We chose the anterior axillary line as our entry site and threaded the catheter 5 cm towards the right shoulder. Before awakening and extubation, each patient received 0.4 cc/kg of 0.5% BUP with epinephrine 1:200,000 (time 0). Patients were then randomized to receive either a continuous infusion of plain BUP 0.25% at 0.125 cc/kg/hr or repeat bolus injections of BUP with epinephrine (0.4 cc/kg) q 6 hrs. Patients in both groups were oriented to the use of patient controlled analgesia (PCA) equipment in the recovery room. Morphine (MS) dosages were set at bolus 0; continuous 0; PCA 1 mg q 5 minute lockout. Patients were encouraged to use the PCA as needed for RUQ pain. Patients in the continuous infusion group had blood samples for free MS and BUP drawn at hours 6 and 24. In addition, visual analog scale (VAS) pain scores were also obtained q 6 hours. Patients in the bolus group had their IPCs injected every 6 hours. Blood samples were drawn immediately before and 30 minutes after the 6 and 24 hour injections. VAS scores were also obtained at q 6° both prior to and 30 minutes after each injection. Twenty four hour PCA usage logs were printed from all patients to document the number of demands for MS made and the amount of narcotic the patient actually received. Statistical significance was analyzed by two way analysis of variance for repeated measures, the Tukey-Kramer post-hoc test, and the unpaired Student's t test with a p value less than 0.05 considered significant. Data is expressed as mean ± standard deviation.

Results: No patient suffered a complication from catheter insertion, drug injection or infusion. Among the patients receiving continuous infusions, demand for and receipt of MS averaged 36 ± 33 attempts and 23 ± 19 mg over 24°. VAS scores averaged 2.7 ± 2. Among the patients receiving bolus injections, demand for MS was 60 ± 23 attempts; receipt, 38 ± 12 mg. VAS scores prior to and 30 minutes post injection averaged 5.75 ± 2.4 and 1.55 ± 1.3. No significant difference between groups was found in total MS demand or receipt, blood levels of free MS or BUP or post injection VAS scores as compared to scores from the infusion group. Pre-injection VAS scores were significantly higher than the infusion and post-injection scores. Along with the perception of increased pain in the two hour period before IPC injections, patients in the bolus group tended to increase their demand and receipt of PCA MS significantly. Of note is that one patient in the bolus group achieved a venous blood BUP concentration of 4.7 mcg/ml with no signs or symptoms of toxicity.

Discussion: The manpower requirements for repeated bolus IPC injections can be prohibitive. An anesthesiologist must be available to assess the patient's degree of pain, provide additional medication, and watch for signs of toxicity. The q 6 hour re-injection schedule corresponds to our clinical impression of the frequency for repeat dosing. This also corresponds with reported durations of adequate analgesia in a similar dose range[2]. A continuous infusion of IPC BUP safely and effectively provides good post-cholecystectomy pain relief. The technique is at least as beneficial as q 6° bolus injections. In addition, manpower requirements for its use are minimal. Patients can be monitored by floor nurses who assess degree of comfort and potential problems. A steady infusion will also avoid the large bolus injections which may lead to toxic serum levels of local anesthetic.

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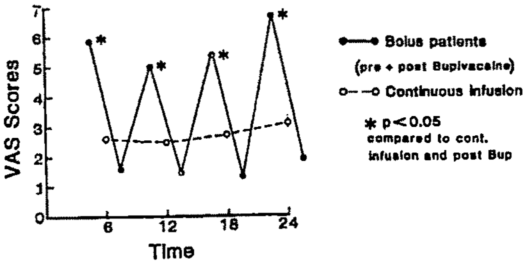

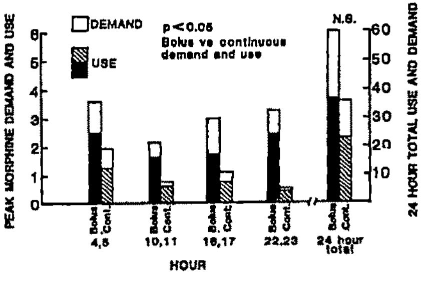

Title: END-TIDAL PCO_2 AS A MONITOR OF CHANGE OF ARTERIAL PCO_2 IN CHILDREN WITH CONGENITAL HEART DISEASE

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Introduction: End-tidal carbon dioxide tension ($PetCO_2$) underestimates arterial carbon dioxide tension ($PaCO_2$) measurement in children with certain congenital heart defects.[1,2] In the studies cited above, the children were examined under hemodynamically stable conditions at a single point in time. The current study was designed to determine the change in the arterial to end-tidal PCO_2 difference (ΔPCO_2) over time in children with congenital heart disease (CHD) to evaluate the efficacy of $PetCO_2$ as a monitor of change of $PaCO_2$.

Methods: With approval from the hospital ethics committee, 40 children > 11 months in age and > 6 kg in weight were studied. All patients were scheduled for corrective or palliative cardiac surgery.

Infants and children were classified according to their cardiopulmonary diagnosis as determined from physical, echocardiographic and/or angiographic examinations. These children were classified on the basis of their pulmonary blood flow (PBF) as: acyanotic with no intracardiac anomaly (normal, n = 10); acyanotic with increased PBF (acyanotic-shunting, n = 10); cyanotic with decreased PBF (cyanotic-shunting, n = 10); and cyanotic with normal or increased PBF (mixing, n = 10).

All children were studied at normothermia in the supine horizontal position after induction of anesthesia and intubation. Distal $PetCO_2$ was sampled continuously using a Puritan-Bennett/Datex model 253 infrared analyzer calibrated prior to each use. Simultaneous $PetCO_2$ recordings and $PaCO_2$ measurements were obtained during 5 events:

(1) placement of arterial line (control);
(2) patient preparation (time 1);
(3) post-sternotomy (time 2);
(4) post-heparin administration (time 3); and
(5) aortic cannulation (time 4).

Statistical significance was determined using one-way and repeated measures ANOVA and the Tukey test for multiple comparisons with $p \leq 0.05$.

Results: There was no significant difference in the distribution of ages among the 4 groups (Table). The weight in the control group was significantly greater than in the other 3 groups ($p < 0.05$). The figure depicts the ΔPCO_2 over time for each group. At the events designated as 3 and 4, ΔPCO_2 in the children with cyanotic-shunting lesions were significantly different ($p < 0.05$) as compared to their control (event 1).

Discussion: These data suggest that although $PetCO_2$ measurements are reliable as a monitor of change of $PaCO_2$ in patients with acyanotic shunting (increased PBF) and mixing (normal or increased PBF) cardiac lesions, $PetCO_2$ is inappropriate as a monitor of change of $PaCO_2$ in children with cyanotic shunting (decreased PBF) cardiac lesions.

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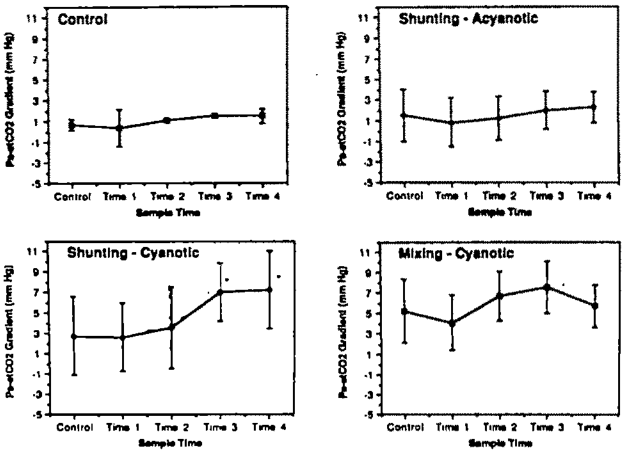
TABLE

	AGE (yrs) *	WEIGHT (kg) *
NORMAL	9.1 ± 6.2	33.4 ± 19.6 †
ACYANOTIC	5.1 ± 4.8	18.7 ± 14.9
CYANOTIC	3.4 ± 2.0	13.5 ± 3.3
MIXING	5.2 ± 2.8	17.2 ± 6.4

* Mean ± S.D.
† p<0.05

FIGURE



*p < 0.05 different from control values

Title: EFFECT OF RANITIDINE ON GASTRIC FLUID IN CHILDREN UNDERGOING REPAIR OF CONGENITAL HEART DISEASE

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Introduction: Recent studies have reported the safety and efficacy of ranitidine therapy in decreasing gastric acidity in children.[1,2] Preoperatiave oral administration of ranitidine at 2 mg/kg significantly increased gastric fluid pH and decreased gastric fluid accumulation in children before non-cardiac surgery.[3] Children undergoing cardiopulmonary bypass (CPB) are at increased risk for stress induced gastric ulceration. The effect of oral premedication with ranitidine on gastric fluid pH and volume in response to CPB has not been examined. We therefore studied the effect of preoperative oral ranitidine on the gastric fluid pH and volume in children undergoing elective repair of congenital heart disease (CHD).

Methods: This prospective, randomized study was approved by the local ethics committee. Informed written consent was obtained from the parents/guardians of all children. Twenty-four children > 1 year of age and > 7 kg in weight admitted for elective repair of CHD were randomly assigned to one of three oral regimens: Group 1: placebo; Group 2: 2 mg/kg ranitidine; Group 3: 4 mg/kg ranitidine. The drug was administered orally together with 5 ml/kg of apple juice 4 hours prior to surgery. All children received usual preoperative medication of pentobarbital (2 mg/kg) orally 90 minutes preoperatively and morphine (0.2 mg/kg) with atropine (0.02 mg/kg) intramuscularly 30 minutes preoperatively. After induction of anesthesia and at the end of surgery prior to transfer to the intensive care unit (ICU), an orogastric tube was inserted into the stomach and gastric fluid was aspirated for volume and pH measurement. The pH of the aspirate was measured using an Accumet pH meter 900 calibrated prior to each use. Gastric fluid pH was also measured, with indicator strips (pH 0-6), up to 12 hours post-surgery in the ICU. White blood cell counts and corresponding differentials were compared pre- and 1 week post-administration of ranitidine. Statistical significance ($p < 0.05$) was determined using Kruskall Wallis and Mann-Whitney U-tests.

Results: There was no significant difference in weight, volume of gastric aspirate, white blood cell count nor differential among the three groups at any time during the study (Table). The pH of the gastric aspirate of the control group was significantly less than the groups which received ranitidine. In the groups receiving ranitidine, the pH of the gastric aspirate at 12 hours was significantly less in the 2 mg/kg group than the 4 mg/kg group and was not statistically different from the control group (Figure).

Discussion: These data suggest that preoperative oral ranitidine at 2 mg/kg effectively maintains gastric fluid pH above 2.5 throughout surgery and into the post-operative period for children undergoing CPB. This preliminary report concludes that oral ranitidine in either 2 or 4 mg/kg dose is a safe and efficacious regime for children undergoing CPB who warrant such prophylactic measures.

Acknowledgement: The authors wish to thank Glaxo Canada, Inc. for their support.

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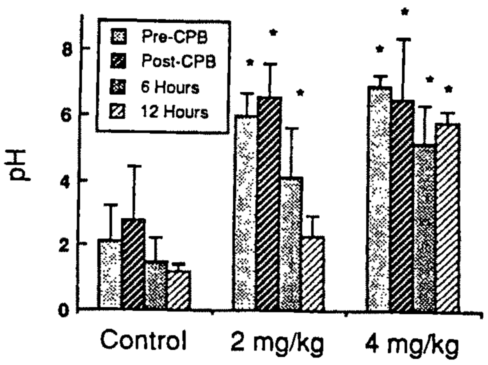
TABLE

	Control	2 mg/kg	4 mg/kg
Weight (kg)	17.2 ±15.2	15.1 ±3.25	12.2 ±3.3
Volume Pre-CPB (ml/kg)	0.59 ±0.24	0.32 ±0.23	0.2 ±0.15
Volume Post-CPB (ml/kg)	0.79 ±0.53	0.39 ±0.31	0.86 ±0.68
WBC Pre-CPB (x1000)	9.76 ±4.42	9.3 ±1.24	8.23 ±2.9
WBC at 1 week (x1000)	11.54 ±2.88	11.5 ±2.47	9.18 ±3.00
PMN Pre-CPB (x1000)	5.35 ±2.94	4.61 ±1.30	3.23 ±1.00
PMN at 1 week (x1000)	6.87 ±1.99	6.28 ±1.17	4.81 ±2.15
Lymphs Pre-CPB (x1000)	3.54 ±2.2	3.87 ±1.3	4.25 ±2.89
Lymphs at 1 week (x1000)	3.3 ±1.13	3.09 ±1.56	3.01 ±1.72

Abbreviations: WBC, white blood cell count;
PMN, polymorphonuclear count
Lymphs, lymphocyte count
CPB, cardiopulmonary bypass

FIGURE



* $p < 0.05$ compared to control and 2 mg/kg at 12 hours

Title: THE IDENTIFICATION OF FACTORS PREDICTIVE OF ANESTHESIOLOGY RESIDENT OUTCOME.

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Introduction. The reliable selection of those applicants who will turn out to be the "better" anesthesiology residents has long plagued resident selection committees. Prior studies have noted the lack of relationship, specifically, predictive power, between applicant interview assessment and resident performance[1-3]. Prior studies specifically evaluating anesthesiology resident outcome have been sparse[4,5], and largely unsuccessful in identifying "predictive" factors for future "success". These studies have focused for the most part on academic predictors, such as test scores and grades. Clinical impression however suggests that nonacademic predictors play a significant role in the success of residents.

The present study was undertaken to determine whether or not certain measurable psychological factors are identifiable at the time of resident application which may be predictive of future resident "success".

Methods. Following approval of the Review Committee on Investigations Involving Human Subjects, 10 senior anesthesiology faculty members were asked to rank all 30 second and third year anesthesiology residents from "best" to "worst". First year residents were excluded because faculty members did not know them as well. All rankings were averaged, and the faculty members interviewed individually to specifically determine what they considered to be the characteristics of the top ten "best" residents, as well as those of the "worst" ten residents. Many of the factors they identified coincided with the personality traits of the 16PF Personality Questionnaire[6], a widely used measure of personality. After written informed consent was obtained, residents were then administered the 16PF. Results focus on the broad personality profile of anesthesiology residents, univariate differences on each scale as well as multivariate predictors of group membership in the top ten or worst ten. The factors evaluated were age, the 16 "primary" personality traits, 8 broader "secondary" traits, and 2 distortion/validity scales.

Results. Although no one factor based on a one-way analysis of variance singly distinguished between the top, middle, and worst groups, when the factors were evaluated together (in a multivariate model), significant findings emerge. A stepwise discriminant function analysis identified 11 factors that when taken together predicted group membership with 100% accuracy ($p < .003$). In order of descending magnitude of importance, the following 11 factors are described in the direction that the top group scored in: Analytical/socially polished (Factor N), assertiveness (Factor E), sensitivity (Factor I), emotional maturity (Factor C), self-controlled (Factor Q3), restrained/serious (Factor F), tense (Factor Q4), trusting/team worker (Factor L), self-confident (Factor O), older, and less of a tendency to present themselves in a negative light (negative distortion scale).

Discussion. Anesthesiology residents judged to be the "best" by faculty who have worked closely with them, appear to be psychologically quite different than those judged to be the "worst". Results suggest that one can reliably predict who will be the successful anesthesiology resident based on the scores on the identified factors of this personality test, and on age. Given the relative stability and permanence of personality traits, evaluation of resident's scores on pre-admission, can give the Resident Selection Committee another important "window" into future performance. The successful anesthesiology residents appear to be socially and emotionally mature individuals, who are assertive yet sensitive, and who are self-controlled and restrained. They appear to be more well-adjusted psychologically. The small sample size however limits the interpretation of results and hampers the appropriateness of using discriminant function analysis. Our data point to the need for further work on non-academic factors as predictors of resident outcome, particularly with large samples and in a longitudinal prospective design.

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Title: THE DIFFERENCE IN THE TOLERANCE OF LEFT VENTRICULAR MUSCLES OF YOUNG AND MIDDLE-AGED RATS TO RELATIVE HYPOXIA

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Introduction. Reduction of extracellular oxygen tension brings a marked effect on myocardial contractility in mammals(1). It has been known that the young of many species appears able to survive in the absence of oxygen for prolonged time periods when compared with adults, because heart of the young has more glycogen stores and a shift in the lactate dehydrogenase isoenzyme pattern. In fetus and newborn, fetal hemoglobin might play a role, too. A relatively large quantities of glycogen preserves both electrical and mechanical activity during hypoxia by anaerobic breakdown of carbohydrates. But some of the results from other studies showed no differnces(2,3). It is our clinical impression that myocardial susceptibility to damage from hypoxia is greater in aged patients than younger ones because there is progressive functional decline in cardiovascular system, as well as other organs, with getting old. The aim of the present investigation was to study the effect of 3 different concentrations of oxygen (12.5, 25, 50%) on myocardial contractility of young and middle-aged rats, so as to demonstrate in-vitro presumably the increased susceptibility of senescent cardiac muscle to hypoxia.

Methods. The protocol was approved by the institutional animal investigation committee. The isometric contractions of isolated rat left ventricular papillary muscles were studied in an oxygenated muscle bath at the temperature of 35°C. The muscles were then indirectly stimulated at a frequency of 0.25 Hz. At the maximum muscle length of the length-tension curve(Lmax) of each preparation, 18 muscles from 2 months old rats(young group; YG) and eight 12-14 months old rats(middle-aged group; MG) were exposed to 3 different concentrations of oxygen(12.5, 25, and 50%). The effects of different oxygen concentration were computed as the differences between the observed measurements, and control measurements obtained with the control gas mixture of 95% oxygen and 5% carbon dioxide before administration of different oxygen. The following measurements were made in all experiments: peak developed tension(Tpd); resting tension(Tr); maximum rate of tension development and relaxation(±dp/dt); time to peak tension(TPT); time for tension to decay 90% of maximum($RT_{90\%}$).

Results. The effects of decreasing concentrations of oxygen on isometric contraction showed gradual depression in both age groups in Tpd, +dp/dt, and -dp/dt from control values(Table 1). The degrees of depression were greater in YG than MG. The differences for Tpd, +dp/dt, and -dp/dt among the subgroups(12.5, 25, 50%) were statistically significant except Tpd between 25 and 50% subgroups in MG. For Tr, TPT, and $RT_{90\%}$, there was one significant diminishing of Tr in 25% value in MG and no significant change in TPT, but there were significant changes in 12.5 and 25% values in YG.

There were statistically significant depression of Tpd, +dp/dt, and -dp/dt in relation to oxygen concentration in both age groups with exception of +dp/dt and -dp/dt for 50% oxygen in MG. The depression ranged from -25 to -49%/-14 to -38%, -22 to 45%/-1 to -27%, and -27 to -45%/-3 to -32% for YG/MG in Tpd, +dp/dt, and -dp/dt respectively. In addition, the depression was significantly greater in YG than MG. All of these effects were progressively greater with decreasing oxygen concentration.

For the changes in Tr, TPT, and $RT_{90\%}$, there were no drastic changes except of progressively increasing $RT_{90\%}$ with increasing oxygen concentration which was more significant in YG.

Discussion. This study revealed that the middle-aged rats showed better tolerance to decreasing oxygen supply than the young ones. It is obvious that the old one has more stiffened and thicker papillary muscles and usually believed that the mechanical properties are likely to be affected by differences in oxygenation of the inner core of the muscle strip. However Heller & Whitehorn(4) didn't find any difference in terms of myocardial contractility between two different age groups. It might be suggested that, besides this resistance to inner core hypoxia, the myocardium of MG could get a lot of experiences to hypoxia with advancing ages and consequently improve its tolerance to hypoxia.

Surprisingly, this study showed the depression of contractility even though the oxygen concentration is higher than 21%. We always consider it safe if we do not lower the oxygen concentration below 33% during anesthesia. But, to myocardium, especially for the one who has low cardiac reserve, is it really safe?

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Table 1. Effects of Decreasing Concentration of Oxygen on Isometric Contractions of Isolated Rat Heart Muscle

Oxygen conc.		Tpd	+dp/dt	-dp/dt	Tr	TPT	$RT_{90\%}$
12.5	YG	-48.3 ± 12.3*	-44.9 ± 13.5*	-45.4 ± 13.4*	12.1 ± 20.8	- 3.6 ± 8.2	27.3 ± 22.8*
	MG	-37.9 ± 8.8*	-26.9 ± 10.3*	-31.9 ± 16.2*	- 4.0 ± 3.4	-11.0 ± 9.5	10.7 ± 18.3
25	YG	-35.8 ± 12.0*	-30.4 ± 8.4*	-40.0 ± 13.3*	3.9 ± 11.6	- 4.9 ± 9.0	15.6 ± 15.0*
	MG	-18.9 ± 12.7*	- 3.8 ± 3.8*	-12.8 ± 6.7*	-15.2 ± 12.5*	- 3.8 ± 7.3	0.6 ± 5.6
50	YG	-24.8 ± 12.7*	-21.7 ± 9.2*	-27.0 ± 10.8*	- 4.9 ± 14.5	- 5.0 ± 6.3	5.5 ± 10.7
	MG	-13.6 ± 10.1*	- 1.4 ± 9.0	- 2.9 ± 16.5	- 4.0 ± 3.9	- 3.1 ± 9.2	3.7 ± 5.8

Data are mean ± S.D. of per cent changes from control * ; $p < 0.05$
YG; young group; MG; middle-aged group Tpd; peak developed tension
±dp/dt; maximum rate of tension development & relaxation Tr; resting tension
TPT; time to peak tension $RT_{90\%}$; time for tension decay 90% of tension

TITLE: UPTAKE OF LORAZEPAM BY SCIMED OXYGENATOR MEMBRANE

AUTHORS: P Leong, M.D., DA Rosen, M.D., KR Rosen, M.D.
AFFILIATION: C.S. Mott Children's Hospital, Pediatric Anesthesiology, Univ. of Mich., Ann Arbor, MI 48109

INTRODUCTION: To provide amnesia, lorazepam is often supplemented as an adjunct to high dose narcotic anesthesia during cardiac surgery upon initiation of cardiopulmonary bypass. Decreases in circulating narcotic levels during cardiopulmonary bypass (CPB) greater than hemodilution alone have been reported.[1] *In vitro* studies with fentanyl, sufentanil, and midazolam have shown a specific drug absorptive ability of the SciMed oxygenator membrane.[2,3] The purpose of this study was to determine the interaction of lorazepam with the oxygenator membrane using a previously validated *in vitro* model.

METHODS: Serial dilutions of C_{14} lorazepam 30,60,120,300,600 and 3,000ng/ml were prepared with Normoso 1-R (abbot labs). The pH was adjusted to 7.4 at 37°C, and all experiments were carried out at 25° C. Multiple 1cm^2 pieces of membrane were cut and the exact surface area was calculated using the known density provided by the membrane manufacturer. All lorazepam analysis was performed using liquid scintilation techniques.

Experiment #1 Maximum uptake of Lorazepam by the Membrane: 2ml of C_{14} lorazepam with each of the above concentrations were placed in test tubes. A 1cm^2 piece of membrane was then incubated without agitation in each of the test tubes for 24 hours. A similar experiment was repeated with agitation for 24 hours. A tube containing 2ml of Normosol-R with 1 cm^2 membrane and no lorazepam was used as a control. Solution samples as well as membranes were assayed for lorazepam.

Experiment #2 Membrane Uptake of Lorazepam with Time: A control sample containing 2ml Normosol-R and membrane were assayed at time=0. Membranes squares were then placed in 2ml of 30,60,300,600 ng/ml of lorazepam solutions, agitated membranes and solutions were assayed at 5 in 10,30, 60,90, and 120 minutes.

RESULTS: As shown in Figure 1 the maximum uptake of lorazepam on the membrane is linearly dependent on the concentration of lorazepam in the solution. When exposed for 24 hours there were no differences between the agitated and unagitated samples. Figure 2 shows the uptake of lorazepam over time for different concentrations. Ninety percent of uptake occurs within 60 minutes in these aggitated samples.

DISCUSSION: This is the first study to demonstrate the potential for uptake of lorazepam by the membrane in the SciMed oxygenator during C.P.B. The pharmacokinetic and pharmacodynamic action of lorazepam in the nonbypass setting has been reported by Greenblatt et al.[4] There exists a potential for subtherapeutic plasma levels of lorazepam if great amounts are taken up by the membrane oxygenator. Our experiments utilizing isolated membrane squares consistently demonstrated the specific ability of the SciMed membrane to bind lorazepam. In addition, this uptake is concentration dependent. Uptake is demonstrated when the membrane is exposed to the clinically relevant plasma levels of 30 to 600ng/ml of lorazepam. Agitation of the solution does not effect binding of the lorezepam when the membranes are in contact for prolonged periods of time, but is essential for shorter periods in order to minimize boundary layer phenomenon. The accuracy and validity of isolated membrane studies to reflect uptake by the intact C.P.B. has been previously reported only for fentanyl. Lorazepam appears to interact differently with the membrane than fentanyl, (and presaturation of the membrane appears to be impractical because of the tremendous uptake potential by the SciMed membrane). The interaction of a patient with the C.P.B. is a complex clinical phenomenon, and other factors such as reversibility of binding, effect of protein binding and effect of multiple compartments need to be determined in order to apply this to the clinical setting. Additionally these results apply only to the SciMed ® brand of membrane oxygenators and should not be generalized to other makes of membrane oxygenators.

FIGURE 1: Maximum membrane uptake of Lorazepam with different concentrations

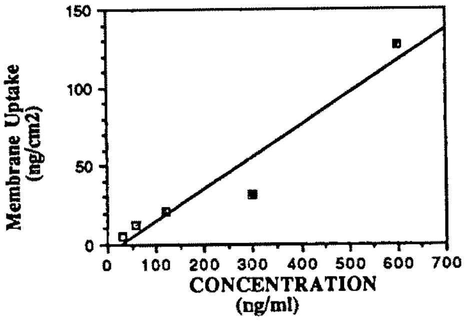
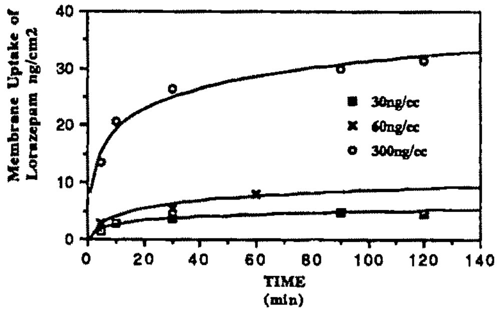


FIGURE 2: Membrane Uptake of Lorazepam over Time



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Title: HEMODYNAMIC OBSERVATIONS OF OCFENTANIL (A-3217) IN PATIENTS WITH ISCHEMIC HEART DISEASE.

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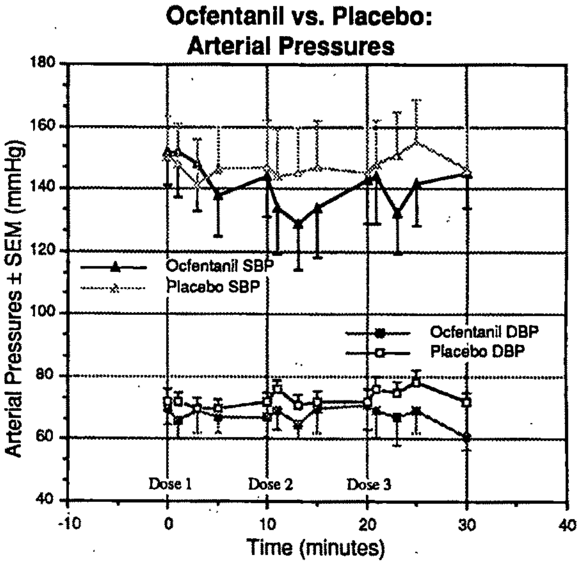
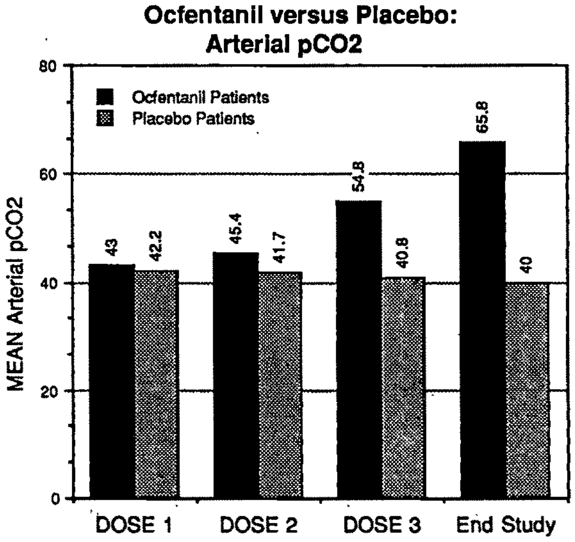
INTRODUCTION: Ocfentanil (A-3217) is a naloxone reversible piperidine hydrochloride with greater potency but a slightly shorter duration of action than fentanyl. The data from animals studies (rats & dogs) indicate that ocfentanil may be an effective anesthetic agent. In dogs anesthetized with ocfentanil and isoflurane, the highest dose of ocfentanil (18 µg/kg) resulted in reductions of MAP (62%), HR (86%), and CO (70%). In relation to dose-dependent respiratory depression, the therapeutic index of ocfentanil was consistently greater than that of fentanyl. Since ocfentanil is more potent, an equi-analgesic dose of fentanyl may be expected to produce a greater cardiovascular effect. This study was designed to assess the hemodynamic and ventilatory changes after incremental doses of ocfentanil up to 5.0 µg/kg in patients with significant coronary-artery disease.

METHODS: This study was approved by the Institutional Review Board and all patients gave written informed consent. The study was performed in 12 patients in a double-blind, randomized, placebo controlled, balanced, parallel design protocol. All subjects were ASA III patients with EF's greater than 30% scheduled for elective CABG surgery with no history of MI within 1 week, hemodynamic instability, or recent narcotic administration. All subjects were premedicated with diazepam (0.1 mg/kg PO) and scopolamine (0.2 mg IM), and the routine invasive monitoring lines were inserted (2 IVs, intra-arterial catheter, Swan Ganz). Patients were also monitored utilizing continuous EEG and ST-segment analysis. After 15 minutes of stabilization, the patients received incremental intravenous right-atrial bolus-doses of either ocfentanil (Drug=D) in doses of 0.5, 1.5, and 3 µg/kg every 10 minutes (total dose 5.0 µg/kg) or equal volumes of normal saline (Control=C) at the specified times. Hemodynamic variables were recorded every 15 seconds with an on-line computer data collection system (Archive). ABGs were measured at baseline and 10 minutes after each drug dose. Arterial histamine levels were determined by RIA following each dose. Following completion of the study protocol, the subjects were anesthetized with sufentanil and the anesthetic management for CABG-surgery proceeded in routine fashion. The recorded hemodynamic parameters were grouped and analyzed for significance ($p<0.05$) by two-way repeated measures analysis of variance and t-test with Bonferroni adjustments.

RESULTS: There were minor differences in the group demographic variables (age: 59 yrs - D, 53 yrs - C; EF: 45% - D, 56% - C) with the ocfentanil group slightly older and with smaller EF's. The baseline hemodynamic parameters were not statistically different. The grouped, dose-related systemic arterial hemodynamic changes are shown in Graph 1. Following dose 2, there was a slight decrease in SVR which became significant after the 3rd dose. There were no significant changes in the grouped pulmonary artery pressures until after the 3rd dose of ocfentanil (maximum differences 10 minutes after last dose: PAS 40 vs 29 mmHg; PAD 26 vs 19 mmHg). PVR did not change significantly. HR did not change over time, however, and CI did increase significantly in the ocfentanil group over time. All of the ocfentanil patients did require ventilatory assistance by mask shortly after the 3rd dose. Arterial oxygenation remained excellent with the patients receiving 100% FIO2 by face mask. The arterial CO2's are shown in Graph 2. The CO2 changes would have been greater without the administration of minimal ventilatory assistance in each ocfentanil subject. The 2nd or 3rd dose caused at least transient loss of eyelid-reflex in all patients, as well as typical narcotic-induced EEG changes. Ocfentanil did not cause any measurable increases in histamine levels. All the patients tolerated the study and subsequent anesthesia and CABG-surgery without complications.

DISCUSSION: In patients with ischemic heart disease, ocfentanil did produce mild dose-related decreases in arterial blood pressure with elevated arterial CO2 at the time of maximal sedation and analgesia. Subjects lost consciousness after 2.0 µg/kg, and all of the ocfentanil patients developed transient apnea. There was a possible episode of rigidity following the 3rd dose in one subject. Despite hypercarbia and increased PA pressures, patients maintained hemodynamic performance. Many of the hemodynamic changes recorded during this study are more likely secondary to the narcotic-induced hypercarbia and not direct drug effects. The cardiovascular profile following ocfentanil administration, especially if the ventilation is assisted or controlled appropriately, suggests ocfentanil may produce safe and adequate anlagesia in the clinical setting. This question is currently under investigation by infusing the drug intravenously at a constant rate until loss of eye-lid reflex while controlling ventilation.


Ocfentanil vs. Placebo: Arterial Pressures


Ocfentanil versus Placebo: Arterial pCO2

Title: HEMODYNAMIC OBSERVATIONS OF PENTAMORPHONE (A-4492) IN PATIENTS WITH ISCHEMIC HEART DISEASE.

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INTRODUCTION: Pentamorphone (A-4492) is a thebaine derivative which has been shown to be 500 times more potent than morphine in man. In healthy volunteers, doses of 0.1 - 0.2 µg/kg produce good analgesia with minimal respiratory depression lasting 1 hour.(1) Doses of 0.24 µg/kg produce mild depression (45 min) while doses of 0.72 µg/kg produce significant depression of both the hypoxic and hypercapnic response.(2) Healthy volunteers had minimal hemodynamic changes from low doses of Pentamorphone. This study was designed to assess the hemodynamic and ventilatory changes after incremental doses of Pentamorphone up to 1.0 µg/kg in patients with significant coronary-artery disease.

METHODS: This study was approved by the Institutional Review Board and all patients gave written informed consent. The study was performed in 12 patients in a double-blind, randomized, placebo controlled, balanced, parallel design protocol. All subjects were ASA III patients with EF's greater than 30% scheduled for elective CABG surgery with no history of MI within 1 week, hemodynamic instability, or recent narcotic administration. All subjects were premedicated with diazepam (0.1 mg/kg PO) and scopolamine (0.2 mg IM), and the routine invasive monitoring lines were inserted (2 IVs, intra-arterial catheter, Swan Ganz). Patients were also monitored utilizing continuous EEG and ST-segment analysis. After 15 minutes of stabilization, the patients received incremental intravenous right-atrial bolus-doses of either A-4492 (Drug=D) in doses of 0.1, 0.3, and 0.6 µg/kg every 10 minutes (total dose 1.0 µg/kg) or equal volumes of normal saline (Control=C) at the specified times. Hemodynamic variables were recorded every 15 seconds with an on-line computer data collection system. ABGs were measured at baseline and 10 minutes after each drug dose. Arterial histamine levels were determined by RIA following each dose. Following completion of the study protocol, the subjects were anesthetized with sufentanil and the anesthetic management for CABG-surgery proceeded in routine fashion. The recorded hemodynamic parameters were grouped and analyzed for significance ($p<0.05$) by two-way repeated measures analysis of variance and t-test with Bonferroni adjustments.

RESULTS: There were no differences in the group demographic variables (age: 53 yrs - D, 58 yrs - C; EF: 54% - D, 56% - C) or baseline hemodynamic parameters. The grouped, dose-related systemic arterial hemodynamic changes are shown in Graph 1. Following dose 2, there was a significant decrease in SVR. There were no significant changes in the grouped pulmonary artery pressures until after the 3rd dose of Pentamorphone (maximum differences 10 minutes after last dose: PAS 48 vs 26 mmHg; PAD 22 vs 11 mmHg). As expected from these data, PVR increased following the 3rd dose of drug. HR and CI did not change significantly in either group over time. Two patients did require transient ventilatory assistance by mask (< 2 minutes) shortly after the 3rd dose of Pentamorphone. Arterial oxygenation remained excellent with the patients receiving 100% FIO2 by face mask. The relation between the arterial CO2's and the increasing PAD are shown in Graph 2. The final dose caused at least transient loss of eyelid-reflex in all patients, as well as typical narcotic-induced EEG changes. Pentamorphone did not cause any measurable increases in histamine levels. All the patients tolerated the study and subsequent anesthesia and CABG-surgery without complications.

DISCUSSION: In patients with ischemic heart disease, Pentamorphone did produce dose-related decreases in arterial blood pressure with elevated arterial CO2 at the time of maximal sedation and analgesia. Subjects lost consciousness after 1.0 µg/kg, and only 2 of the 6 treated patients developed transient apnea. Despite hypercarbia and increased PA pressures, patients maintained hemodynamic performance (i.e. CI) and respiratory efforts. The relationship between acute elevations in CO2 and the PAD should be further investigated. Many of the hemodynamic changes recorded during this study are more likely secondary to the narcotic-induced hypercarbia and not direct drug effects. The cardiovascular profile following Pentamorphone administration, especially if the ventilation is assisted or controlled appropriately, suggests Pentamorphone may produce safe and adequate anlagesia in the clinical setting.

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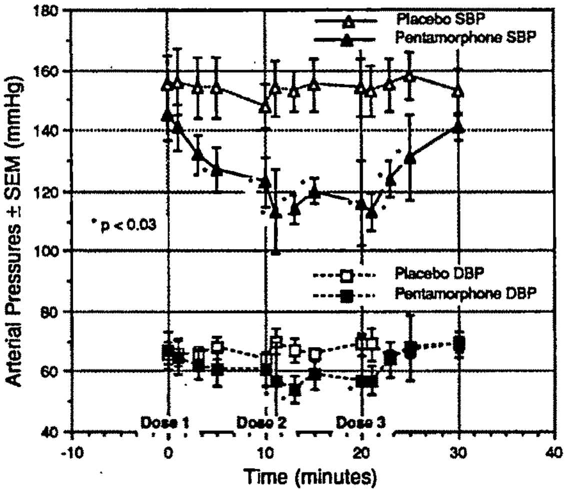
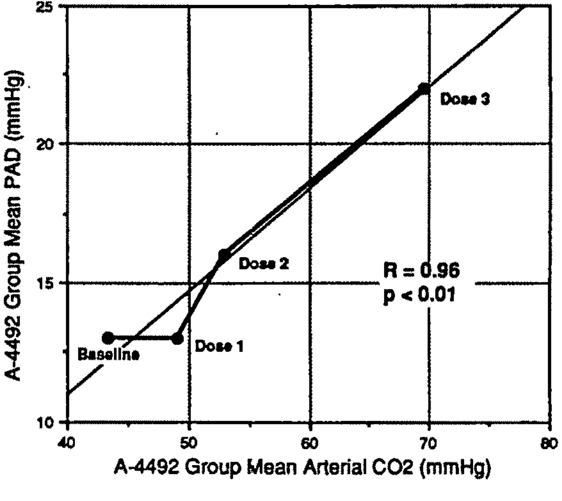
Graph 1: Pentamorphone vs. Placebo: Arterial Pressures



Graph 2: Pentamorphone Dose Effects on Arterial CO2 and Pulmonary Artery Pressure



Title: TRANSESOPHAGEAL ECHOCARDIOGRAPHY: PREDICTION OF INTRAOPERATIVE HYPOVOLEMIA

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Introduction. Transesophageal echocardiography is gaining increasing use intraoperatively as a monitor of ventricular function and volume. Recent evidence suggests that end-diastolic and end-systolic areas measured using a single imaging plane of the left ventricle (LV) at the level of the short axis view correlate well with estimates of LV volume from first-pass radionuclide angiocardiograms (1). No previous study, however, has compared the usefulness of preload estimation from TEE to other routinely obtainable hemodynamic parameters in predicting hypovolemia. To assess the relationship between TEE-preload parameters and routine hemodynamic parameters such as heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), pulmonary artery diastolic pressure (PAD) and central venous pressure (CVP), we continuously measured TEE and hemodynamic variables, and determined the relationship between acute changes in TEE-preload and acute changes in hemodynamic parameters in patients undergoing coronary artery bypass graft (CABG).

Methods. After institutional approval and informed consent was obtained, 139 men scheduled for elective CABG were included in the study. Following tracheal intubation, a gastroscope tipped with either a 3.5 or 5 MHz phased array transducer was introduced into the esophagus and maintained at the level of the papillary muscles to obtain a short axis view of the LV. TEE data were continuously recorded onto videotapes during both the pre- and postbypass periods in 50 patients, and during the prebypass period only in 89 patients. The videotapes were scanned both in real time and stop-frames for evidence of low LV volume. When such an episode of low LV volume was detected, the videotape was backtracked every 5 min to determine the exact onset time of the episode. The criteria for low volume include: complete obliteration of LV cavity at end-systole, or near obliteration of LV cavity when the papillary muscles apposed each other at end-systole. HR, SBP, DBP, PAD and CVP were recorded continuously onto hard-copies from induction to the early ICU period. Hemodynamic parameters recorded at 5 and 10 min after, and at the onset of low LV volume were compared to those recorded at 10 min before the onset (controls). A significant change in hemodynamics was defined as an acute change of >10% compared with control.

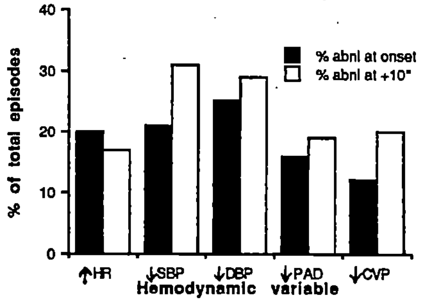
Results. 40/139 patients (29%) had 62 episodes of low LV volume. No significant changes in HR, SBP, DBP, PAD, or CVP occurred at the onset or at 5 or 10 min after the onset of low volume episodes (table 1).

Overall, during low LV volume, only 20% of the episodes was associated with increased (>10%) HR; or with decreased SBP-21%, DBP-25%, PAD-16%, and CVP-12% (FIG 1-dark bars). At 10 min after the onset, 17% of HR increased; 31% of SBP, 29% of DBP, 19% of PAD, and 20% of CVP decreased >10% compared to onset (FIG 1-open bars). Furthermore, 35% of HR actually *decreased*; 44% of SBP, 46% of DBP, 16% of PAD, and 18% of CVP actually *increased* during low LV volume.

Table 1
Hemodynamics 10", 5" before, 5" and 10" after, and at onset of low LV volume (means ± SEM)

	-10"	-5"	ONSET	5"	10"
HR	64±3	66±3	71±2	70±3	68±3
SBP	112±5	117±5	115±4	114±5	112±5
DBP	58±3	59±3	61±2	59±2	58±3
PAD	11±.9	11±.7	11±.5	11±.7	11±.6
CVP	6±.9	6±.7	6±.6	6±.7	7±.9

FIG 1 Hemodynamic changes during low LV volume



Discussion. Our study demonstrated that:
1) Hypovolemia detected by TEE as low LV volume was common in patients undergoing CABG surgery.
2) The appearance of low cardiac volume was infrequently preceded by any acute alteration in hemodynamic parameters (HR, SBP, DBP, PAD and CVP).
3) Routine hemodynamic monitoring in assessing volume may actually be misguiding, since in a substantial number of episodes, hemodynamics changed in the opposite direction of that expected.

Thus routine measurements of HR, systemic and pulmonary BP, or CVP appear to be insensitive measures of low LV volume. TEE may provide early and sensitive estimates of cardiac volume.

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Title: ALCOHOL AFTER MIDAZOLAM SEDATION: DOES IT REALLY MATTER?

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Introduction. In one study, six percent of ambulatory surgery patients drank alcohol within 24 hours after their operations.[1] Anesthesiologists must be concerned about this because alcohol could have additive effects in impairing psychomotor performance with drugs given during anesthesia. With ambulatory surgery patients, midazolam is frequently used as an intravenous sedative because of its short elimination half-life. We conducted the following study to determine whether midazolam would interact with alcohol that was drunk four hours after a midazolam injection.

Methods. Sixteen healthy male volunteers (23.6 ± 3.1 yr, 68.1 ± 10.1 kg) participated in a double-blind, randomized, placebo-controlled, cross-over trial. This study was approved by our institutional clinical investigation committee and written consent was obtained from each subject. The subjects were studied 4 times successively with a one-week wash-out period between trials. Each test day the subjects randomly received by slow intravenous injection (30 s) either saline placebo or midazolam (0.1 mg/kg). Four hours after injection, the subjects drank over a twenty minute period either juice placebo or alcohol in juice (0.7 g/kg). Blood alcohol concentration was measured indirectly from breath air using the Alco-Sensor III (Intoximeters, Inc., St. Louis) breath analyzer. Before injection, and one, three, five and seven hours after the injection, the following psychomotor skills were assessed: auditory or visual reaction time (the subjects pressed the space-bar on a computer keyboard after hearing a sound or seeing a letter); body sway (a computerized strain gauge measured force displacement); action judgment mistakes (using a steering wheel, subjects tried to keep two pointers on a moving track without striking objects); eso/exophoria. Repeated measures analysis of variance was used to assess the effects of midazolam alone and of midazolam with alcohol.

Results. Midazolam caused a significant impairment in auditory and visual reaction time, sway, action judgment mistakes and eso/exophoria (all $p < 0.001$, except sway $p < 0.005$). Mean ± SD blood alcohol concentration 1 hour after ingestion was 0.056 ± 0.013%. In most states, a motorist with a drug alcohol concentration of 0.1% is driving under the influence of alcohol. Alcohol caused a significant impairment in sway, action judgment mistakes and eso/exophoria (all $p < 0.005$). There was no interactive effect between midazolam given 4 hours prior to alcohol and alcohol. The figure illustrates the effect of midazolam and alcohol on exophoria.

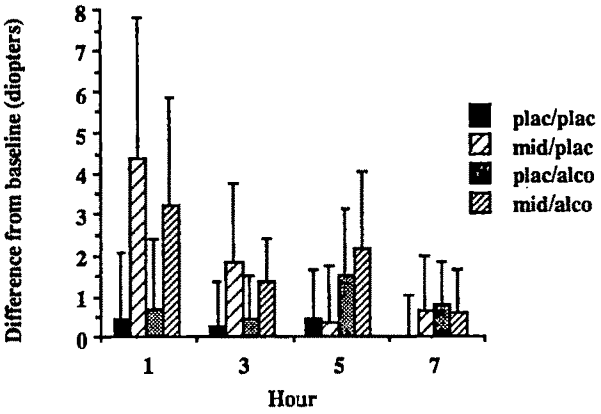

Figure. Exophoria after midazolam and/or alcohol. The x-axis indicates hours after injection of midazolam. Subjects drank alcohol at hour 4. The y-axis indicates the change from baseline in diopters.

Discussion. As expected, midazolam and alcohol each have an effect on psychomotor performance. When alcohol is ingested four hours after midazolam is administered, however, the effect of alcohol is not increased by midazolam. Because ambulatory surgery patients usually receive additional drugs such as narcotics and/or general anesthesia, we are conducting additional studies to see if other drugs, individually or combined, will interact with alcohol and to determine the interval after drug injection at which alcohol will have an effect.

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Title: DISTRIBUTION, ELIMINATION AND ACTION OF VECURONIUM IN ELDERLY SURGICAL PATIENTS

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Introduction. The normal physiological changes that accompany aging have been shown to prolong the effect of long acting muscle relaxants.[1] Conflicting results have been reported for vecuronium (VEC), a relaxant of intermediate duration. D'Hollander, in a dose-response study found the action of VEC prolonged in patients over age 60.[2] Rupp, who simultaneously studied the pharmacokinetics and pharmacodynamics of VEC in elderly patients, reported that the clearance and volume of distribution of VEC were decreased.[3] Since in Rupp's study the elimination half life and the plasma concentration at 50% paralysis were no different in the elderly than in younger controls, he concluded that "healthy elderly patients do not appear to represent a population distinctly different from younger adults in their pharmacokinetic/pharmacodynamic response." In an attempt to clarify these conflicting reports we undertook a study of distribution, elimination and action of VEC in elderly surgical patients.

Methods. After obtaining institutional approval and informed consent, eight controls (26-48 yr) and seven elderly (72-86 yr) patients were studied. General anesthesia was induced with fentanyl 4-7 µg/kg, droperidol 0.6-2.5 mg, and thiopental 2.5 mg/kg and then maintained with N_2O-O_2 (70-30%) and fentanyl 2-3 µg/kg/hr. The response of the adductor of the thumb to supramaximal stimulation of the ulnar nerve at the wrist (frequency 0.1 Hz, duration 0.15 ms) was recorded. An IV bolus of VEC (0.1 mg/kg) was given and the patient intubated. Arterial blood samples were obtained at 1, 3, 5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300 and 360 min. Additional samples were drawn between the timed kinetic samples if return of twitch warranted obtaining another sample. Plasma was separated, frozen and later analyzed by a spectrofluorometric method.

The times to 5, 25, 50 and 75% recovery of twitch height were recorded. Plasma concentration time course curves for each patient were fitted to both bi- and triexponential equations, using weighted, nonlinear least squares regression analysis. The best fit for the data was then determined using the F ratio test. Pharmacokinetic parameters were calculated by using standard methods for bolus IV injection of a drug. Pharmacokinetic parameters, the time to 50% recovery and the recovery indexes (5-25% and 25-75%) were compared between elderly and controls by Student's t-test (two-tailed). $P < 0.05$ was considered significant. The linear portions of the log plasma concentration-response curves between 20% and 80% paralysis for the two groups of patients were compared by analysis of covariance.

Results. Plasma decay curves for VEC in both groups were best described by biexponential equations. The elderly patients demonstrated a significantly longer time to recovery of 50% twitch and prolonged recovery indexes (5-25%, 25-75%) (Table I). Kinetically, the elderly exhibited a significantly prolonged elimination half life ($t_{1/2}$ elim). Comparison of the plasma concentration-response relationship for VEC showed no significant difference between elderly and control patients.

Discussion. The data from this study supports d'Hollander's observation that the action of VEC is prolonged in elderly patients. Moreover, we found the elimination half life of VEC in the elderly is significantly prolonged. Since there was no difference between the concentration-response relationship for either group the prolonged action of VEC in the elderly appears related to pharmacokinetic changes. Since the elimination of VEC is highly dependent on hepatic clearance, the prolonged $t_{1/2}$ elim and prolonged duration of action of VEC in the elderly may be related to the decrease in splanchnic blood flow that accompanies age.[4,5] Our results contrast with that of Rupp who, not observing a prolongation of the elimination half-life of VEC in the elderly concluded that the action of VEC in the elderly did not differ from the young controls. This study differs from Rupp's in that VEC was given as a bolus and a N_2O analgesic anesthetic technique employed whereas Rupp used an infusion technique with anesthesia maintained by N_2O-halothane.

The results of this study together with d'Hollander's work suggest that anesthesiologists should expect the action of VEC to be prolonged in the elderly surgical patient.

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Table 1. Vecuronium Kinetics and Dynamics (Mean ± SD)

	Young	**Elderly**	**P**
$t_{1/2}$ elimination (min)	78±21	130±57	.031
V_i (l/kg^{-1})	0.075±.02	0.08±.01	.574
Vd_{area} (l/kg^{-1})	0.49±.1	0.44±.1	.387
Clp (ml/kg^{-1}/min^{-1})	5.0±3	2.5±.7	.058
T 50% Recovery (min)	39.8±14	97.1±29	.001
5-25% Recovery (min)	10.7±5	27.8±18	.032
25-75% Recovery (min)	15.0±8	49.4±11	.001

Title: DOSE-ENCEPHALOGRAPHIC RESPONSE TO FENTANYL IN MAN

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Introduction. The electroencephalogram (EEG) has proven to be a powerful tool in the study of drug effect upon the brain. This study was designed to determine the effect of varied doses of fentanyl (FEN) in man on multiple descriptors of frequency and power derived from power spectrum analysis (PSA) of the EEG.

Methods. After obtaining institutional approval and informed consent, 21 patients aged 20 to 58, were studied. All patients were ASA class I or II, had no evidence of hepatic, renal or CNS disease and were on no chronic narcotic or benzodiazapine medication. Premedication consisted of glycopyrolate 0.2 mg IM one hour prior to the study. EEG leads were placed in the F_3-C_3 (anterior) and P_3-O_1 (posterior) positions.

After preoxygenation, anesthesia was induced with thiopental, 4 mg/kg and succinylcholine 1.5 mg/kg. The trachea was intubated, anesthesia was maintained with N_2O-O_2 (70-30%) and ventilation adjusted to maintain normocarbia. Relaxation was maintained with vecuronium.

The data collection system consisted of a modified PSA device which digitizes the EEG signal, performs a Fast Fourrer Transformation (FFT) of the data and transfers the FFT data to a MAC Plus computer for storage and further analysis. Once the EEG had stabilized, 25-40 min after the induction of anesthesia, the study was begun. A 5-min baseline EEG was obtained and then the patients received one of the four dosages of FEN (1, 5, 10 or 20 µg/kg) and EEG data was collected for another 10-15 min. The data was later analyzed to derive 25 descriptors of power in various frequency bands and spectral edge frequencies (SE) between 50 and 97%. Descriptors were obtained from 30 second time periods (15 averaged 2-second epochs). For comparison between patients, the data were then normalized by taking the control value for each descriptor as 100. The normalized dose-response points for each descriptor were analyzed by linear regression and their correlation coefficients (r) derived. In addition, these dose-response curves were compared with those previously obtained for sufentanil.[1]

Results. The spectral descriptor that gave the best correlations between the various doses and responses was SE97% (r = 0.76), while the r of SE90% was 0.71. Among the power bands examined, delta (.5-3.5 Hz) produced the best correlation between the dose of FEN and response (r = 0.78). The mean increase in power in delta produced by the various doses of FEN was: 115% at 1 µg/kg, 308% at 5 µg/kg, 1037% at 10 µg/kg and 4189% at 20 µg/kg. FEN 1 g/kg caused a decrease of SE97% of 15% from the control, 5.0 µg/kg a 27% decrease, 10 µg/kg a 45% decrease and 20 µg/kg, a 77% decrease from the control. In contrast to results reported in a previous study,[1] the r's of the regression lines of the posterior EEG montage were similar to those obtained with the anterior montage. When the log dose-response curves from SE97% and SE90% in patients given FEN were compared with patients in a previous study who had been given sufentanil under similar experimental conditions, the regression lines were parallel and the doses of the two narcotics differed by a factor of 10.

Discussion. Several studies of the effects of narcotics on the EEG in man have been reported.[2-5] These studies have, however, involved the EEG reponse to either a single dose or an infusion of FEN. In this study, EEG changes in response to four doses of FEN were examined. Increased power in the delta band correlated well with increased doses of FEN. The changes in SE97% also correlated well with increasing doses of FEN and when compared with spectral edge changes observed in a previous study employing sufentanil appear to reflect the analgesic potency of these two narcotics (7-10:1, respectively). Thus it appears that spectral edge frequencies derived from PSA of the EEG may reflect the analgesic potency of various narcotics.

All this information is of value when the EEG is used either in pharmacodynamic studies of narcotics or to monitor drug effect on the brain.

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Title: IMPROVED HEMODYNAMIC AND RENAL FUNCTION WITH CLONIDINE IN CORONARY ARTERY BYPASS GRAFTING

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INTRODUCTION:

Clonidine is a centrally acting alpha$_2$ and weak peripheral alpha$_1$ adrenergic agonist with sedative and antihypertensive actions. It has been shown to decrease fentanyl and Isoflurane requirements in humans and to contribute to hemodynamic stability.[1,2] Previous clinical research in humans has been non-blinded. There are no reports in the literature of the effects of clonidine on renal function following cardiac surgery, although renal failure in this population is associated with a mortality rate of 67%.[3]

METHODS:

With institutional investigational approval and patient informed consent, 17 controlled hypertensive patients with good left ventricular function were enrolled in this study. Patients were randomized into two groups, receiving either clonidine 3 ug/kg and lorazepam 40 ug/kg or placebo and lorazepam 40 ug/kg orally 90 minutes preoperatively. Patient and anaesthetist were blinded as to which premedication the patient received. The patient's usual cardiac medications were also given where appropriate. After arrival in the operating room, patients were given additional I.V. lorazepam for overt anxiety while routine non-invasive cardiac surgical monitors and an arterial line were placed. After preoxygenation, a priming dose of pancuronium was administered and anesthesia was induced with a titrated dose of sufentanil to loss of consciousness. Pancuronium, to a dose of 0.15 mg/kg was given to facilitate intubation. Post induction a fiberoptic mixed venous pulmonary artery catheter was inserted. Heart rate and blood pressure were maintained within 15% of preoperative baseline values with boluses of sufentanil up to a total of 10 ug/kg. Further blood pressure control was obtained with Isoflurane, up to 1% end tidal concentration. After cardiopulmonary bypass inotropes and vasodilators were added at the discretion of the anesthetist.

Hemodynamic function was monitored throughout the surgery and post operatively in the cardiac surgical intensive care unit (CSICU). Values were recorded preoperatively, on arrival in the O.R., pre and post induction, post sternotomy, pre and post bypass and hourly for three hours in the CSICU. Serum creatinine concentrations were recorded preoperatively, daily for three days and at one week post operatively. Data were analyzed for significance using a chi-square and Student's t-test with significance being defined as a P value of less than 0.05.

RESULTS: (See Tables)

There were no demographic differences between the two groups regarding age, weight, gender, severity of disease or preoperative medical therapy. We found that patients given clonidine required significantly less sufentanil at induction and Isoflurane during anesthetic maintenance, had significantly fewer episodes of hypertension or tachycardia intraoperatively, and had significantly higher cardiac indexes with lower heart rates post bypass. There were no differences in preoperative creatinine concentrations in the two groups however, post operatively, those patients given placebo had significant persistent elevations of serum creatinine concentrations while those given clonidine did not. There was no difference in intraoperative diuretic therapy between the two groups and while those in the clonidine group tended to have higher urine output on bypass this did not achieve statistical significance.

DISCUSSION:

With a blinded investigational protocol, we were able to confirm previous non-blinded studies showing reduced anesthetic requirements and improve hemodynamic stability with the use of clonidine as a premedication. Post cardiac surgery renal failure is multi-factorial and associated with a high mortality.[3] We report a salutary effect of clonidine premedication with demonstrably improved post operative renal function. These findings may shed light on the pathophysiology of perioperative renal failure and may indicate another method for the intraoperative preservation of renal function.

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TABLE ONE

	Clonidine	Placebo	
Sufentanil Inc (mcg/kg)	2.5 ± .36	4.4 ± .99	P < 0.05
Isoflurane (MAC Hours)	0.4 ± .6	1.8 ± 1.1	P < 0.05
Episodes Hypertension	1	5	P < 0.05
Episodes Hypotension	4	2	N.S.
Episodes Tachycardia	1	4	P < 0.05
Postbypass Heart Rate	84 ± 4	92 ± 4	P < 0.05
Postbypass Cardiac Index	3.9 ± .3	2.9 ± .2	P < 0.05

TABLE TWO

	Clonidine	Placebo	
Preop Creatinine	112 ± 30	116 ± 58	N.S.
$\frac{\text{Day 1 Creatinine}}{\text{Preop Creatinine}}$	1.03 ± .06	1.06 ± .1	N.S.
$\frac{\text{Day 2 Creatinine}}{\text{Preop Creatinine}}$	1.04 ± .1	1.19 ± .09	P < 0.05
$\frac{\text{Day 3 Creatinine}}{\text{Preop Creatinine}}$	0.98 ± .17	1.30 ± .26	P < 0.05
$\frac{\text{Day 7 Creatinine}}{\text{Preop Creatinine}}$	0.99 ± .11	1.36 ± .4	P < 0.05

Values are mean ± standard deviation

Title: ORAL TRANSMUCOSAL FENTANYL CITRATE FOR ANALGESIA AND ANXIOLYSIS IN THE EMERGENCY ROOM

Authors: GH Lind, M.D., MA Marcus, M.D*., MA Ashburn, M.D., SL Mears, M.D., B Petersen, TH. Stanley, M.D.

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Introduction

Emergency Room (ER) medical care frequently involves the management of painful conditions. Unfortunately the use of parenteral narcotics in patients, particularly children, can cause additional pain and anxiety. Previous studies have shown that oral transmucosal fentanyl citrate (OTFC) produces analgesia and sedation in adult volunteers (1) and anxiolysis in children before operation (2). This prospective, pilot study was undertaken to evaluate the ability of OTFC to provide noninvasive and nonthreatening analgesia and anxiolysis for painful ER procedures and conditions.

Methods

Ten ASA class I patients with an extremity fracture or a laceration, abcess or wound requiring debridement have been studied. Approval of the institutional human research committee and written, informed consent was obtained. The mean age was 23.5 years with a range of 6 to 34 years. Blood pressure, heart and respiratory rates and oxygen saturation by continuous pulse oximetry (SaO_2) were measured and recorded every 10 minutes for at least 60 minutes after starting OTFC. Pain, cooperation and sedation scores (Table 1) were recorded at baseline and every 2 minutes for 30 minutes. OTFC was administered at a dose of 12-20 mcg/kg. Patients were instructed to rapidly consume the unit by active licking without biting or chewing. Patients were asked to report the onset of analgesia and any adverse symptoms. If the SaO_2 dropped below 90% the patient was verbally stimulated. Discharge criteria were met when patients were awake and alert with normal vital signs for 2 hours after OTFC and the SaO_2 was >90% without supplemental oxygen. The data were analyzed for statistical significance using the Wilcoxon signed rank and paired Student's t tests. $P<0.05$ was considered statistically signficant.

Pain Score:
1. No complaint of pain.
2. Complains of minimal pain.
3. Complains of pain.
4. Crying from pain but able to be consoled or complains of severe pain.
5. Crying form pain and not easily consoled or complains of extreme pain

Sedation Score:
1. Asleep, not easily aroused.
2. Asleep, slowly responds to verbal instructions.
3. Drowsy, readily responds to verbal instructions.
4. Awake, calm.
5. Awake, crying.

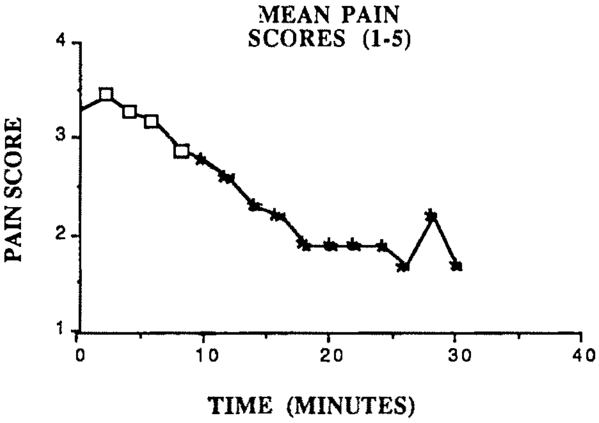
Cooperation Score:
1. Cooperative.
2. Resistant, requires minimal or no restraint.
3. Thrashing, requires active restraints.

Results

Baseline pain was moderate or severe (score 3-5) in all 10 patients. Over the 30-minute data collection period pain scores improved in all patients and mean scores decreased from 3.4 (±0.7 S.D.) to 1.7 (±0.7 S.D.)(Fig. 2). Pain scores were decreased by 3 in 3 patients, by 2 in 2 patients, by 1 in 4 patients and was unchanged at 30 minutes in 1 patient. Nine of 10 patients were complaining of minimal or no pain (score 1-2) after 30 minutes. Mean sedation scores decreased significantly from 4.1 at baseline to 3.4 30 minutes after OTFC. The mean fentanyl dose was 13.7 mcg/kg. Because of the onset of complete analgesia within 26 minutes one patient didn't consume the entire OTFC unit.

Statistically significant but clinically unimportant decreases in respiratory rate (17.8 to 15.8 mean) and systolic blood pressure (122 to 115 mean) were present 60 minutes after starting the OTFC compared to baseline. Other vital sign values were unchanged from baseline over the observation period. Mild facial pruritus not requiring treatment occurred in 4/10 patients. Mild nausea of approximately 1 minute duration occurred in 1/10 patients and resolved without treatment. 1/10 patients had nausea with vomiting requiring anti-emetic therapy. Transient desaturation to 83% occurred in 1/10 patients and responded to verbal stimuli. No patients required naloxone or oxygen therapy.

OTFC was readily accepted and provided effective analgesia in all patients. Physicians in the ER rated OTFC's efficacy the "same or better" when compared to routinely employed alternative therapies (parenteral narcotics) in 10/10 patients.



*Significantly different from baseline (P < 0.05)

Dicussion

These data indicate that OTFC can produce significant analgesia and anxiolysis and appears to be as safe as parenteral narcotics routinely employed in the ER. Our findings suggest that additional, carefully controlled, prospective clinical trials should be undertaken to more precisely define the role of OTFC in the ER.

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Title: ANAESTHESIA DECREASES A HORMONE MEDIATED THRESHOLD FOR NAUSEA AND VOMITING

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Introduction: The incidence of nausea and vomiting after laparoscope ovum retrieval has been reported as 54%. An increased incidence of nausea and vomiting around the time of menses has recently been demonstrated suggesting a hormonal influence(1). Furthermore, the estrogen levels of women who experience nausea and vomiting after laparoscopic ovum retrieval has been shown to be significantly greater than in those who do not(1). The present study compares the incidence of nausea and vomiting after laparoscopic ovum retrieval in patients receiving general anaesthesia and those having a neurolept anaesthetic.

Methods: After institutional review approval, we reviewed the anaesthetic, post-anaesthetic recovery room and short stay unit records of all patients presenting for laparoscopic or transvaginal ovum retrieval between January 1, 1984 and December 31, 1988. Patient age, weight, type of anaesthetic - including narcotic, inhalational agent and neuromuscular relaxant, type and dose of perioperative antiemetic and presence of nausea and vomiting post operatively were recorded. Hormonal concentrations were obtained from the prospective data bank of the infertility clinic in our institution.

Patients were excluded from the study if the anaesthetic records were incomplete, if they had received preoperative sedation or antiemetic or if hormonal concentrations were not available.

Statistics where descriptive, and by chi square, paired and non-paired T tests were appropriate. Significance was accepted at $P\leq0.05$.

Eighty-five patients were included in the study. All patients underwent several procedures - either laparoscopic and/or transvaginal ovum retrieval. One hundred and thirteen laparoscopic ovum retrievals were performed. Twenty-seven of these were excluded from the study. Eight-four transvaginal ovum retrievals were done. Seven of these were excluded.

All laparoscopies were performed under general anaesthesia. All patients received Fentanyl 0.5-1.5 µg/kg, N_2O - 30%, Isoflurane 0-1% or an equipotent dose of Enflurane. Neuromuscular blockade was accomplished with succinylcholine infusion, atracurium or vecuronium.

Transvaginal ovum retrieval was performed using intravenous Fentanyl 0.5-1.5 µg/kg.

Results: The incidence of nausea and vomiting in the laparoscopy group was 32.5% vs 7.8% in the transvaginal ovum retrieval group $P<.05$.

In patients who underwent laparoscopic ovum retrieval, estrogen concentrations were significantly higher in those who experienced nausea and vomiting post-operatively than in those who did not. Average peak estrogen concentrations were 6162.8 pm/ml in patients experiencing nausea and vomiting vs 4443 pm/ml in those who did not $P<.001$. In patients having transvaginal ovum retrieval, the peak estrogen concentration in the patients who experience nausea and vomiting was 5609 pm/ml vs 3700 pm/ml in those who did not.

Paired analysis of patients who underwent both laparoscopic and transvaginal ovum retrieval shows similar estrogen concentrations in patients experiencing nausea and vomiting after general anaesthesia but not after transvaginal ovum retrieval.(see Figure I)

Discussion: Peak estrogen concentrations are higher in women who vomit after laparoscopy than in women who do not. Although our numbers are small, a similar difference exists in the ultrasound group. This suggests an estrogen effect on the nausea and vomiting reflex arc.

Paired analysis of patients who underwent both laparoscopic and transvaginal ovum retrieval showed that estrogen concentrations were similar when patients vomited after laparoscopy as compared to concentrations when they did not vomit after transvaginal ovum retrieval. We conclude that the threshold for hormone mediated nausea and vomiting is lower in patients undergoing laparoscopic ovum retrieval under general anaesthesia.

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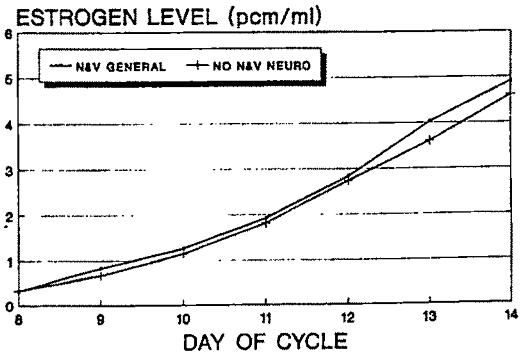
Figure I



Title: **CONTROL OF POSTANESTHETIC SHIVERING BY LOCALIZED REGULATED RADIANT HEAT**

Authors: JM Lipton, Ph.D., T Schroeder, MSIV, P Banish, MSIII, C Whitten, M.D., P Jeffrey, M.D., AH Giesecke, M.D.
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Introduction: Postanesthetic shivering (PAS) and hypothermia are uncomfortable and they may be harmful. Previous research suggests that it is possible to control PAS in subhuman primates(1) and in humans (2) with radiant heat. In the investigations on humans, PAS was inhibited by application of radiant heat solely to the upper torso, neck and lower face, skin regions known to have a high density of warmth receptors that can exert a powerful influence on thermal sensations and on thermoregulatory responses (3,4). The plan in the present studies was to test the efficacy and safety of such localized radiant heat in controlling shivering but with a new heating device that allows precise adjustment of power dissipation, distance of the heat source from the patient, and the setting of a feedback temperature control circuit that senses sternal skin temperature.

Methods: The study was approved by the local Institutional Review Board. Shivering patients entering the recovery room were randomly assigned to receive control treatment, the standard warmed blanket alone, or radiant heat plus the warmed blanket. Records of shivering were made using electrodes placed over pectoral and trapezius muscles and a Grass Medical Instruments (Quincy, MA) model 7D polygraph. The radiant heat source was six infrared bulbs in two parallel rows in the order (anterior-posterior) 125, 250, 125W. Current to the lamps was adjusted so that the power dissipation of the lamps was 750W. A fail-safe dual thermistor probe sensed temperature of the skin over the sternum. The circuit was adjusted to maintain sternal skin temperature at 41°C. The upper torso was covered with one layer of bedclothes only. The radiant heat source centered 18 in. above the sternum was turned on only after a clear record of shivering was obtained (1-5 min). Only patients who showed clear signs of shivering were included in the study. Student's t test with Bonferroni correction for multiple tests was used to compare differences.

Results: There were no significant differences ($p > .05$) in patient characteristics, duration of surgery or in initial temperatures of experimental and control groups. With application of radiant heat cessation of shivering, confirmed by both EMG recordings and visual observations, occurred within 14 min in 15 (83%) of the 18 patients, whereas only 1 (7%) of 15 patients in the control group had stopped shivering by this time. At the end of the 30 min. test period five patients (33%) in the control group were still shivering, whereas only one patient given radiant heat continued to shiver. The average duration of shivering in control patients (mean 24.8 ± 1.4 SEM min) was significantly greater ($p < .0001$) than that for patients who received radiant heat (8.8 ± 2.3 min). There was no significant difference ($p > .05$) in sublingual temperatures of the two groups at the end of the 30 min test period. All patients were conscious and the psychological effect of warming was great; 80% of the patients made positive statements about the warmth and/or complained when the heat was turned off. No burns were found on the test day or during an interview the next day.

Discussion: These results, obtained with an apparatus designed specifically for the purpose, confirm that localized regulated radiant heat can be used to control PAS. PAS can be detrimental: it induces a marked increase in metabolism (5) and heart rate (6) and can result in hypoxemia (7), and metabolic acidosis (8). Hypothermia and PAS can be influenced by warm ambient air (9), thermal ceilings (10), reflective drapes (11), warmed anesthetic gas (12) and warmed fluids (13). PAS can also be controlled with drugs (14). The use of localized radiant heat to control PAS obviates unacceptably increasing ambient temperature in the operating room and the cost of installation of thermal ceilings. Unlike most other patient-directed methods, it requires no prior preparation and can be applied only to those patients that show PAS. Unlike drugs, its effect is under direct and immediate control.

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Title: Cerebral Washout of Desflurane vs Isoflurane and Halothane from Rabbit Brain

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Introduction. The low solubility of desflurane (I-653) in blood (1) (blood/gas partition coefficient of 0.42) and tissues (2) indicates that washout of the agent and recovery from this agent should be extremely rapid. Rapid washout of desflurane from the lungs has been documented (3). These data imply that washout of desflurane from brain should be more rapid than that for isoflurane or halothane. However, such a determination has not been made. Here we present data using in vivo magnetic resonance spectroscopy to compare washin and washout of desflurane vs isoflurane and halothane from the rabbit brain.

Methods. After obtaining approval from the UCSF Committee on Animal Research, three New Zealand White rabbits, weighing 4-5 kg, were anesthetized by intramuscular and intravenous injection of methohexital, inhalation of 70% nitrous oxide, and local infiltration of 1% lidocaine. After insertion of intravenous and intraarterial catheters, a tracheostomy was performed. To expose a 2-2.5 cm diameter circle of dura, a craniectomy was performed. Intravascular volume was supported with infusion of lactated ringers (4ml/kg/hr) and paralysis accomplished with pancuronium. Ventilation was mechanically controlled to maintain P_aCO_2 between 35-45 mm Hg. Rectal temperature was maintained between 37-40° C using a servo-controlled water jacketed cradle. The relative cerebral concentrations (CC) of halothane, isoflurane and desflurane were measured from spectra acquired at 188.2 MHz on a 4.7 Tesla Nalorac® spectrometer. For each anesthetic, it was assumed that the CC was proportional to the cerebral partial pressure (i.e. that Henry's Law is obeyed (4)). A 1.0 cm diameter, two-turn radiofrequency surface detection coil with a balanced matched circuit was centered over the exposed dura. A reference bead containing potassium fluoride was placed above the coil and served as both a chemical shift and numerical integration reference. After obtaining a baseline record, nitrous oxide was discontinued. Animals were randomized to receive either a combination of desflurane (4.5%) and halothane (1%) or isoflurane (2%) and halothane (1%) in oxygen from premixed tanks for 30 min. During washin, spectra were acquired for 6 min epochs and inspired (FI) and end-tidal (FA) samples obtained at the midpoint of each. At 30 min, the administration of potent agents was discontinued and anesthesia maintained with nitrous oxide and methohexital (3mg/kg/hr). During washout, spectra were collected in 6 min epochs for the first 30 min, 12 min epochs to 90 min, and one 30 min epoch to 120 min. End-tidal samples were obtained at the midpoint of each. The study was repeated using the second combination of anesthetics. We assumed that end-tidal, arterial, and cerebral partial pressures are equal at 30 min of equilibration, i.e. CC=FAO, the last FA of washin (6).

Results. Washin of desflurane was more rapid than washin of isoflurane and halothane for both the brain (CC/FI) and the lungs (FA/FI). Washout from brain (CC/FAO) and lungs (FA/FAO) was similarly more rapid. A temporal delay was also noted between alveolar and brain concentrations during both washin and washout. Alveolar washout led the washout fromthe brain. This is consistent with uptake and elimination of anesthetics by the remainder of the body.

Discussion. As predicted from relative blood solubility, washin and washout from the brain was most rapid with desflurane. We noted that the washin and washout from the brain paralleled alveolar washin and washout, although with a temporal delay. Our results indicate not only that recovery from anesthesia is more rapid with desflurane than with halothane or isoflurane but also that its residence in the brain is shorter and, as a consequence, seems less likely to produce lingering effects.

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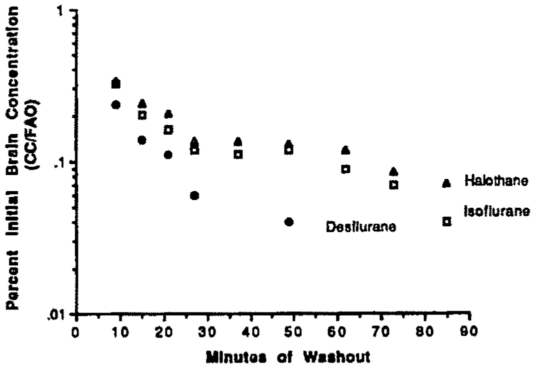

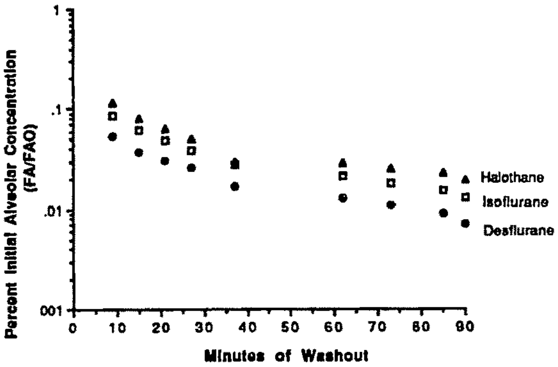

Title: Ventilatory Effects of Desflurane (I-653) in Humans

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Introduction. Desflurane (I-653) is a promising new volatile anesthetic with lower blood and tissue solubilities (1,2) than currently available anesthetics.We evaluated the ventilatory effects of desflurane with and without nitrous oxide in the present study.

Methods. After approval from the committee on human research, informed consent was obtained from 12 male volunteers 20 to 26 years of age. Using local anesthesia,a radial artery catheter was placed. After obtaining baseline measurements of tidal volume (V_t), respiratory rate (RR), and end-tidal CO_2, the ventilatory response to CO_2 was measured using the Read rebreathing technique (3). Volunteers were randomly assigned to receive either desflurane alone (N=6) or desflurane with 60% N_2O (N=6). Anesthesia was induced with desflurane followed by tracheal intubation without muscle relaxants. Alveolar anesthetic levels and $P_{et}CO_2$ were measured with an infra-red analyzer. After a minimum of 10 min of stable end-tidal concentrations, measurements of V_t, RR, $P_{et}CO_2$, arterial and mixed venous blood gases, and ventilatory response to carbon dioxide were made at 1.0, 1.5, and 2.0 MAC. The order of the two lowest concentrations was randomized; for safety, the highest concentration was administered last. For subjects anesthetized without N_2O, alveolar desflurane concentrations were 6%, 9%, and 12% respectively whereas for those who received nitrous oxide, concentrations were 3%, 6%, and 9%.

Results. Desflurane caused a dose-dependent decrease in V_t with a corresponding increase in RR. Although there was no significant reduction in minute ventilation, alveolar ventilation was reduced causing a rise in arterial pCO_2 with increasing depth of anesthesia (fig 1). A decreasing ventilatory response to carbon dioxide was also noted as depth of anesthesia increased (fig 2).

Discussion. Desflurane is a respiratory depressant as indicated by a dose-related increase in resting P_aCO_2 and depression of the ventilatory response to CO_2. Consistent with previous investigations (4,5), the addition of nitrous oxide did not affect resting pCO_2. However, at comparable MAC values, the effect on the response to CO_2 did not differ between desflurane with or without nitrous oxide. A comparison of our data with data for isoflurane, enflurane and halothane suggests that desflurane is not as potent a respiratory depressant as isoflurane or enflurane but has effects comparable to halothane. Moreover, the dose-related changes in tidal volume and respiratory frequency observed indicate that both parameters are useful clinical signs of depth of anesthesia with desflurane.

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Data are reported as mean ± S.E.

Table: Depth of Anesthesia versus Tidal Volume, Resp Rate, Minute Ventilation

O_2	Awake	1 MAC	1.5 MAC	2 MAC
V_t	363±22	235±21	148±22	114±3
RR	15±0.5	24±1.5	26±0.2	32±2
Ve	5.3±0.7	5.5±0.6	3.9±0.5	3.6±0.3

N_2O	Awake	1 MAC	1.5 MAC	2 MAC
V_t	473±70	216±13	153±8	128±6
RR	14±0.5	26±2	32±2.3	40±3
Ve	6.5±1.2	5.7±0.7	5.0±0.7	5.2±0.8

(V_t:(ml), RR:breaths/min, Ve:Minute vent (L))

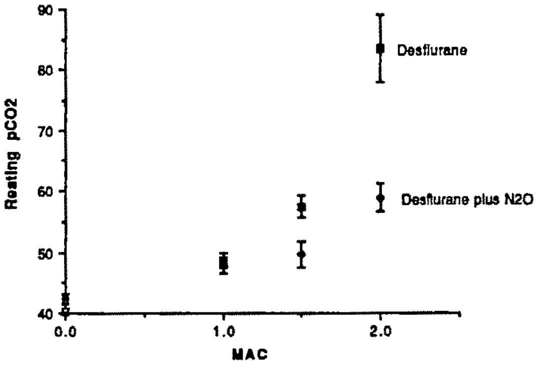

Fig. 1

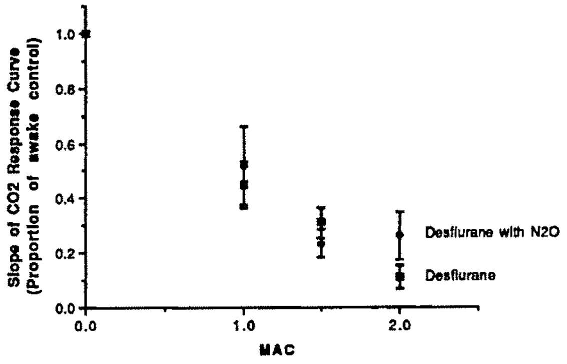

Fig. 2

Title: HELIUM DECREASES THE FLAMMABILITY OF ENDOTRACHEAL TUBES
Authors: RG Loeb, M.D., SG Soriano, M.D.
Affiliation: University of California, Davis Medical Center, Sacramento, California.

Introduction:

Endotracheal tube fires can occur during laser surgery in the airway. It has been reported that helium retards the laser ignition of polyvinyl chloride (PVC) endotracheal tubes better than does nitrogen.[1] This protective effect was observed with a low energy laser beam but not with a high energy beam.

The "oxygen index of flammability" has been previously used to quantify the flammability of endotracheal tubes.[2] It is a measure of the *minimum concentration of oxygen which will support combustion* of a particular material.

This study tests whether helium, compared with nitrogen, decreases the flammability of endotracheal tubes, thereby increasing the safe oxygen concentration threshold. We define a new method to quantify flammability, the diluent-specific "oxygen index of nonflammability". This is the *maximum oxygen concentration, in a specific diluent, which does* **not** *support combustion* of a material. An index of nonflammability is used rather than an index of flammability because the maximum safe concentration of oxygen is of greater clinical importance than the minimum unsafe concentration.

Methods:

Medical grade gases were dispensed at approximately 8 liters per minute from the fresh gas outlet of an anesthesia machine. The fresh gas oxygen concentration was measured with a polarographic analyzer. The gas passed through a mixing chamber containing glass beads and then entered a vertical cylindrical glass combustion chamber. A 3 cm endotracheal tube segment was supported upright in the combustion chamber by a metal clamp. All surfaces of the segment were exposed to the gas. The top surface of the segment was ignited from above by a natural gas flame and the burning segment was allowed to equilibrate for 20 seconds before the oxygen concentration was decreased. The oxygen concentration was decreased by approximately 1 percent every 40 seconds until the flame extinguished or the segment was consumed. When a segment was consumed, it was replaced and testing continued from that oxygen concentration. When the flame extinguished, the oxygen analyzer was allowed to stabilize for two minutes and the concentration was recorded.

The oxygen index of nonflammability in helium or nitrogen was determined for PVC with and without a radiopaque barium sulfate stripe (Hi-Lo ^{R}, Mallinkrodt, Inc., Glens Falls, NY), red rubber (Rusch, Inc., West Germany), and silicon (Fome-Cuf ^{R}, Bivona, Inc. Gary, IN). Each material was tested five times in each gas mixture. The oxygen index for each condition was determined by averaging the oxygen concentrations at which the flame extinguished. Differences between groups were analyzed using unpaired two-tailed t-tests. Significance was accepted at $P<0.01$.

Results:

The oxygen index of nonflammability for PVC with a barium stripe was 0.233 in nitrogen and 0.282 in helium; these were significantly different. PVC without a barium stripe was not significantly less flammable than PVC with a barium stripe. The index for red rubber was 0.185 in nitrogen and 0.207 in helium; for silicon it was 0.198 in nitrogen and 0.211 in helium. These differences in indices between helium and nitrogen were significant for both red rubber and silicon.

Discussion:

It has previously been demonstrated that helium retards the laser ignition of endotracheal tubes[1]; this study demonstrates that it also decreases the flammability of endotracheal tubes. The high thermal diffusivity of helium explains its ability to retard laser ignition[1]; a laser is a metered source of energy and helium dissipates thermal energy better than does nitrogen, so more total energy must be delivered to heat an endotracheal tube to its ignition temperature. It is less obvious that thermal diffusivity would affect flammability, the ability of a flame to propagate. The ability of helium to decrease flammability is greater for PVC than for red rubber, which is greater than for silicon. This may be interpreted to mean that the heat generated by burning silicon in 20 percent oxygen is more than sufficient to ignite adjacent silicon, while with PVC a flame in 23% oxygen generates barely enough heat to ignite adjacent PVC.

This study is methodologically similar to the study of endotracheal tube flammability by Wolf and Simpson.[2] We suggest that our index of nonflammability is conceptually better than their index of flammability because the clinician needs to know the maximum safe concentration of oxygen rather than the minimum unsafe concentration. However, the numerical values of the two indices should be similar.

Pashayan and Gravenstein did not demonstrate a protective effect for helium when endotracheal tubes in 40% oxygen were exposed to a high energy laser beam.[1] Our study demonstrates that helium does protect against high energy ignition, but at lower oxygen concentrations.

Maintaining the oxygen fraction below the oxygen index of nonflammability (i.e. 0.282 for PVC in helium) prevents the possibility of fire even if the endotracheal tube is exposed to a high energy ignition source. The oxygen index of nonflammability for red rubber and silicon is below the ambient oxygen fraction of 0.21.

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TITLE: EFFECT OF INHALATION, NARCOTIC AND NEUROLEPTIC ANESTHESIA ON SEIZURE THRESHOLD IN RATS

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Introduction: Studies examining the differential effects of the inhalation anesthetics on spontaneous electrical discharge at clinically-utilized concentrations demonstrate that halothane and isoflurane are not associated with increased neural firing. At similar concentrations, however, enflurane has been shown to increase neuronal firing in a pattern similar to epileptiform seizures (1). Additionally, reports of patients exhibiting epileptiform seizures under narcotic anesthesia have been published. No study, however, has compared the seizure threshold elicited by an external stimulus for narcotic, neuroleptics, and inhalational anesthetics at similar depths of anesthesia. The purpose of this study was to compare the effects of anesthetics on seizure threshold at comparable anesthetic depths in an animal model of status epilepticus.

Methods: After institutional approval, 105 male Sprague-Dawley rats (275±25 gm) were anesthetized with ketamine 100 mg/kg. The animals were placed in a stereotaxic frame and a midline incision was made on the skull. Screw electrodes were placed in pairs 5 mm from the midline over the frontal and occipital lobes and a reference electrode placed at the midline over the frontal sinus. A tracheostomy was performed and arterial and venous catheters placed in the left carotid artery and right jugular vein, respectively. The animals were ventilated (TV 2.5 ml, RR 90, F_IO_2 1.0) on a Harvard rodent ventilator adjusted to maintain normocapnia utilizing arterial blood gas determinations. Standard limb ECG electrode (lead II) was monitored. Neuromuscular blockade was achieved and maintained using pancuronium. The animals were also given glycopyrrolate 1 mg I.P. to minimize the cardiovascular effects of pilocarpine. The animals were then randomly assigned to one of seven groups (n=15) receiving: 1)halothane 1 MAC; 2)enflurane 1 MAC; 3)isoflurane 1 MAC; 4)ketamine 100 mg/kg; 5)fentanyl 50 mcg/kg; 6)sufentanil 5 mcg/kg, 7)control. After a 30 minute baseline EEG recording period, the animals received pilocarpine HCl 300 mg/kg IP which has been demonstrated to produce status epilepticus mimicking grand mal seizures seen in patients and which are prevented by standard anticonvulsant therapies (2). EEG, ECG, and BP were recorded continuously for 60 minutes following pilocarpine administration, and the time to continuous EEG epileptiform spiking was noted. Data was analyzed using the Kruskal-Wallis H statistic. Secondary testing was done, when appropriate, using the Mann-Whitney U-test. $P \leq .05$ was considered statistically significant.

Results: The time to continuous EEG seizure activity demonstrated a significant prolongation for halothane and isoflurane as compared to enflurane, fentanyl, sufentanil, ketamine and control animals. Enflurane demonstrated a significant prolongation as compared to narcotic, neuroleptic and control animals, but less than isoflurane and halothane. The narcotic and neuroleptic techniques were not different from the control group.

	Time to Seizure (Min.)					
Group	< 14	15-29	30-44	45-59	> 60	Mean(SD)
1.Halothane[a]	0	0	1	5	9	55.1(8.7)
2.Enflurane[b]	0	4	4	3	4	41.7(14.9)
3.Isoflurane[a]	0	0	3	1	11	53.7(11.4)
4.Ketamine	1	9	5	0	0	26.7(7.6)
5.Fentanyl	4	8	2	1	0	21.1(12.5)
6.Sufentanil	6	6	2	1	0	19.8(13.7)
7.Control	1	11	3	0	0	24.3(8.4)

a. 1 and 3, > 2,4,5,6,7; $p < 0.05$.
b. 2 >4,5,6,7; $p < 0.05$.

Discussion: Because the pilocarpine-induced seizure model mimics seizures seen in humans, the influence of anesthetics on seizure threshold in this model is important. Even at relatively low concentrations, anesthetic effect on seizure thresholds was seen. However, no anesthetic technique examined at this dose range, including ketamine, was associated with a lowering of seizure threshold below that associated with the controls although there was a trend in animals receiving narcotics to seize earlier than controls. All three inhalation anesthetics were associated with a higher seizure threshold compared to controls, with enflurane elevating seizure threshold the least. This study demonstrates that even when anesthetic agents are given at therapeutic concentrations, they may significantly alter seizure thresholds and, thus, suggests the importance of selection and monitoring of anesthetic technique in patients exhibiting or prone to seizure activity.

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Title:
EPIDURAL MORPHINE PROVIDES SAFE AND EFFECTIVE ANALGESIA ON HOSPITAL WARDS

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Introduction. Effective pain control, early postoperative ambulation and improved pulmonary function are considered to be major advantages of epidural morphine analgesia (1). Several factors, however, have limited the widespread use of this technique. Bothersome side-effects include pruritus and nausea, while potential risks involve respiratory depression, infection and migration of the catheter into either the subarachnoid space or an epidural vein (2). Some clinicians believe that epidural opiates should only be administered to patients in an intensive care unit where constant observation is possible (3,4).

To make epidural analgesia available 24 hours a day on all hospital wards, we developed an acute pain service. We taught nurses to administer epidural morphine and, under the supervision of an anesthesiology-based pain management service, to vary the dosage and/or the injection time interval to achieve optimal patient comfort. We present our experience with our most recent 1,106 patients using this approach.

Methods. With institutional approval, the following information was collected on daily rounds: 1) the average epidural morphine dose and time interval between injections; 2) patient-assessed pain scores, both at rest and upon coughing/ambulating, using a 0 to 10 verbal analogue scale (0 = "no pain," 10 = "severe pain"); 3) the incidence of pruritus and nausea requiring pharmacologic intervention; 4) the incidence of clinically significant respiratory depression (respiratory rate < 6 breaths/min, as detected by a nurse at hourly checks); 5) the occurrence of catheter migration into an epidural vein as detected by aspiration of blood, or into the subarachnoid space as detected by aspiration of CSF and confirmed by precipitation of thiopentone; 6) the incidence of infection as detected by purulence at the catheter insertion site.

Results. Overall, this report involves 4,343 patient-days and 11,809 epidural catheter injections. Patients ranged in age from 12 to 101 years (50 ± 18).

The characteristics of the patient population and analgesic management are presented in Table 1. The incidence of patients requesting medication to treat pruritus and nausea was 24% and 29%, respectively; 85% of the patients reported mild to no pain at rest on the first postoperative day (Figure 1).

There were two cases (0.18%) of respiratory frequency < 6 breaths/min. Both responded to naloxone administration. Four catheters migrated from the epidural space; 2 (0.18%) into the subarachnoid space and 2 (0.18%) into an epidural vein. All 4 cases were detected by ward nurses prior to narcotic administration; the catheters were removed and the patients were given alternate treatment for pain. There were no incidents of infection related to epidural catheters.

Conclusion. Our experience has demonstrated that, with the education and training of nurses, careful medical supervision and appropriate protocols, epidural morphine can be used effectively and safely to provide superior postoperative analgesia on all hospital wards.

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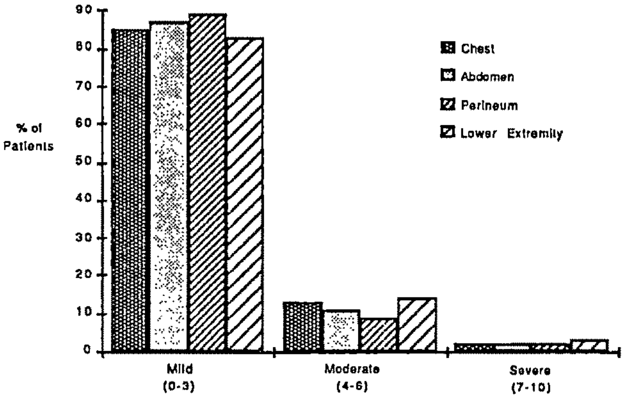
Table 1. Patient Population and Management (Mean±SD).

	Chest	Abdomen	Perineum	Lower Ext
n	146	584	54	322
Age (years)	53±18	50±17	58±19	45±20
Morphine Dose (mg)	4.2±1.4	3.8±1.1	3.3±1.1	3.6±1.9
Interval (hours)	7.9±2.8	8.9±3.4	11.9±6.1	10.7±4.9
Pain at Rest	1.6±1.8	1.4±1.8	1.0±1.9	1.7±2.0
Pain on Cough/Amb	4.7±2.8	4.3±2.6	3.4±3.2	3.9±2.8
Days on Service	5.4±3.1	4.3±3.0	2.4±1.2	2.8±2.0

Figure 1. Distribution of Pain Scores at Rest



Title: EFFECTS OF SEVOFLURANE MAC FACTORS ON BRAIN MICROCIRCULATION IN THE RAT

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Introduction. Sevoflurane (S) has been reported to decrease cerebral blood flow (CBF)(1) and to have similar cerebral effects in comparison to isoflurane.(2) However, little is known concerning its effect on cerebral microcirculation. This study is designed to determine the effects of S by simultaneously monitoring diameter (ID) and red cell velocity (Vrbc) changes in single pial microvessels and changes in calculated volumetric flow ($\dot{Q}$) and intracranial pressure (ICP) at different fractions of minimal alveolar concentration (MAC).

Method. After approval of the institutional animal care committee, female rats (200-250 g, n10) were anesthetized with 2% S and O_2 for surgical preparation. Femoral arterial pressure (BP) was recorded. Blood gases and pH were maintained within normal range by controlled ventilation via tracheostomy. The femoral vein was cannulated for infusion of vecuronium (0.3 mg/kg). A left parietal craniotomy with an encapsulated cranial window was prepared for biomicroscopy and simultaneous recording of ICP changes. Arteriolar ID was measured by image shearing. In selected pial arterioles Vrbc (mm/sec) was measured by the dual-slit photometric method and correlation technique. $\dot{Q}$ ($\times 10^{-3}$ mm^3/sec)(3) was calculated. MAC of S for female rats were determined by a method previously described.(4) The rat was then paralyzed and all parameters were recorded at 0, 0.5, 1.0, 1.5 and 2.0 MAC.

Results. MAC of S for female rats was determined as 1.98 ± 0.07%. At 0.5 MAC, no significant changes in measured parameters were noted. Administration of 1.0 MAC S resulted in a 15% fall in BP ($P = 0.05$) and increase in ID (7.5% $P < 0.05$), ICP (7%) and $\dot{Q}$ (19% $P < 0.05$). At 1.5 MAC there was a 30% decrease in BP ($P < 0.01$) and increase in ID (13% $P < 0.01$), ICP (21%) and $\dot{Q}$ (29% $P < 0.01$). These effects were more pronounced at 2.0 MC (35% decrease in BP, $P < 0.01$; 30.5% increase in ICP; 16% increase in ID, $P < 0.01$; 42% increase in $\dot{Q}$, $P < 0.01$).(Fig.1)

Discussion. The effects of S in the rat resulted in dose related hypotension, pial arteriolar dilatation, increase in $\dot{Q}$ and ICP. However, cerebral hemodynamic stability is maintained if a lower concentration S (0.5 MAC) is used. These findings demonstrate that a vasodilating effect of S is accompanied by an increase in regional CBF during hypotension initiated by S.

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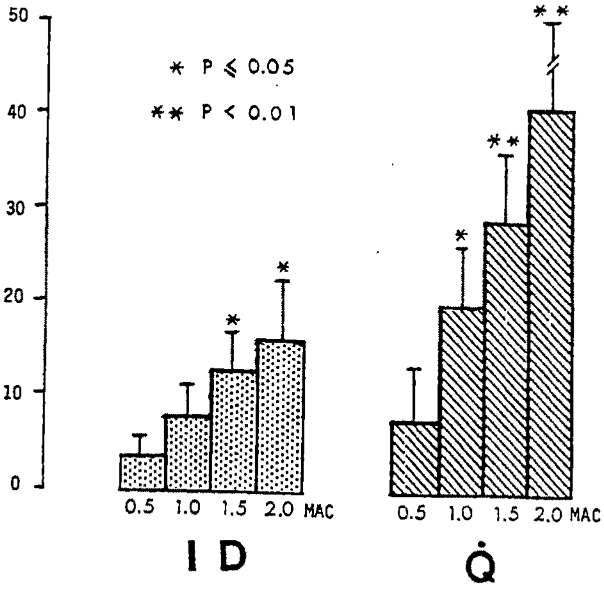

Fig.1 Bar graph represents diameter (ID) and volumetric flow ($\dot{Q}$) changes at different sevoflurane MAC value.

TITLE: COMPARISON OF CONTINUOUS EPIDURAL NARCOTIC BUPIVACAINE MIXTURES TO PATIENT-CONTROLLED ANALGESIA AFTER MAJOR ORTHOPEDIC SURGERY

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Introduction: Epidural narcotic analgesia and patient-controlled analgesia (PCA) are increasingly used as means of controlling pain postoperatively. While each of these techniques has been shown to provide adequate analgesia, few studies have compared these methods in terms of analgesia and side effects. Proper pain management in the postoperative period for patients undergoing total joint replacement is essential for early ambulation so as to hasten recovery and minimize postoperative complications (deep venous thrombosis). The purpose of this study was to compare PCA-morphine sulfate to continuous epidural infusion of morphine sulfate-bupivacaine and fentanyl-bupivacaine for analgesia effectiveness and side effects following major orthopedic surgery of the lower extremities.

Methods: After institutional review board approval, 560 patients undergoing major orthopedic bone and joint surgery between 6/88 and 6/89 of the lower extremities were studied in a prospective fashion. Anesthesia and surgical management of the patients was in accordance with their disease state and accepted practice. Postoperatively, patients received either epidural or patient-controlled analgesia at the discretion of the anesthesiologist. Patients managed with a postoperative epidural infusion received either morphine 0.01% and bupivacaine .1% (EPI-MB, n=94) or fentanyl .001% and bupivacaine .1% (EPI-FB, n=209). Those patients managed with patient-controlled analgesia received morphine sulfate (PCA-MS) with the administration parameters set at 1mg maintenance dose; a 6 minute lockout period, and a 4 hour maximum dose of 20 mg. All patients had their postoperative analgesia maintained for a period of at least 48 hours. Assessment of pain relief and side effects were made daily by an unbiased observer, not involved in this study, for the first two postoperative days. Pain relief was assessed using a Visual Analog Scale (VAS). Side effects that were noted included: nausea and vomiting, pruritus, urinary retension, somnolence, and respiratory depression (defined as a respiratory rate $\leq$ 10). Pain scores were analyzed using ANOVA with repeated measures in one variable (day). Post-hoc testing was done using Tukey-a method. All other data was analyzed using chi-square analysis. P < 0.05 was considered statistically significant.

Results: Patients who received EPI-MB and EPI-FB had significantly lower pain scores than those receiving PCA-MS during the 48 hour study period. The mean dose of morphine sulfate administered by PCA was 28.7mg ± 19.4 mg (range 1mg to 96mg) on day 1, and 33.2 ± 26.0mg (range 0mg to 139mg) on day 2. No patients exceeded their 24-hour limit for morphine by PCA during the study period. The incidence of nausea and vomiting and sedation were not different between groups. Pruritus was significantly higher on the first postoperative day in those patients receiving EPI-MS than PCA-MS. No case of respiratory depression was noted. Urinary retention was significantly higher in those patients receiving EPI-MS than EPI-FB or PCA-MS on Day 2.

	DAY	PCA-MS	EPI-MB	EPI-FB
Pain Score+	1	2.3(2.2)	1.3(2.2)*	1.9(2.4)*
	2	1.5(1.9)	.8(1.7)*	.9(1.7)*
Nausea/ Vomiting	1	15.2	18.4	25.0
	2	7.1	7.9	11.3
Pruritus	1	3.3	14.5*	6.5
	2	3.3	10.5	10.7
Sedation	1	.5	0	.8
	2	.5	2.6	.8
Respiratory Depression	1	0	0	0
	2	0	0	0
Urinary Retention	1	3.5	0	0
	2	2.4	15.0*	0§

+ values for pain scores: means ± (SD)
All other values presented as percentages.
* $p < 0.05$: different from PCA-MS on day.
§ $p < 0.05$: different from EPI-MS on day

Discussion: Epidural administration of narcotics and bupivacaine resulted in significantly better pain scores in patients for postsurgical pain relief after major orthopedic joint and bone surgery. The modest increases in side effects seen in the EPI-MS group may be avoided by using the more lipophyllic FB solution. The incidence of urinary retention is difficult to evaluate in this study because the majority of the patients had foley catheters in place. Neither epidural or PCA was associated with an increased incidence of sedation nor inhibited the patient from early ambulation. In conclusion, epidural narcotic-bupivacaine infusion provided superior analgesia in postsurgical orthopedic patients and mixtures of FB are not associated with a greater incidence of side effects than PCA-MS.

Title: NOREPINEPHRINE RELEASE AND DISPOSITION IN DOG PORTAL VEIN DURING ENDOTOXIN TREATMENT

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Introduction: During endotoxic shock, a marked increase in circulating levels of catecholamines,[1] as well as depletion of peripheral tissue norepinephrine (NE)[2] is observed. Increased circulating NE may result from increased release, decreased uptake or decreased catabolism of NE. Peripheral tissue NE depletion may result from decreased neuronal uptake, increased intraneuronal catabolism, increased release or inhibited synthesis of NE. Previous studies of septic animals have suggested depressed uptake of NE.[3] The aims of this study were to measure the direct effects of endotoxin on 1) basal and stimulation induced release of radiolabeled NE from superfused portal vein, 2) neuronal and extraneuronal uptake and metabolism of radiolabeled NE and 3) on contractile responses during NE release.

Methods: Following approval of the institutional animal care and use committee, portal veins were removed from dogs anesthetized with pentobarbital (30 mg/kg I.V.). The perivascular tissue was dissected away and the vein was cut into a helical strip 2-4 mm wide and 70-100 mm long. The strips were incubated for 1 h in Krebs-Ringer solution containing L-[^{3}H] NE and then mounted in an enclosed superfusion chamber between and in contact with two platinum wire electrodes and superfused at a rate of 2 ml/min with Krebs-Ringer solution (37°C) and allowed to equilibrate for 90 minutes. Following this, Krebs-Ringer containing either 0, 1 or 10 µg/ml of E. coli endotoxin was substituted and continued for the remainder of the experiment. After an additional 120 minutes of superfusion, samples were collected for analysis. A 6 min basal sample was collected. Electric stimulation (ES) was started immediately following and continued for 18 min. On discontinuance of stimulation, an 18 min post-ES sample followed by a 6 min post-ES sample and a 6 min basal sample were collected. ES consisted of rectangular wave impulses (10 V, 2 ms duration, 2 Hz) which has been previously shown to be supramaximal. At the end of the experiment, the tissue was weighed and the [^{3}H] NE and metabolites of NE were extracted. [^{3}H] NE was separated from its metabolites by the method of Graefe et al.[4] Superfusate samples and the effluents and eluates of the chromatographic separations were counted in duplicate using a scintillation counter.

Results:

Release of Total Radioactivity. The addition of endotoxin 1 or 10 µg/ml did not alter the loss of total tritium during basal conditions (17.24 ± 2.95 10^{3} DPM/100 mg), ES (329.58 ± 67.09 10^{3} DPM/100 mg) or in the post-ES period (134.22 ± 29.18 10^{3} DPM/100 mg) as compared to control veins.

Overflow of [^{3}H] NE and Its Metabolites. Endotoxin did not alter the overflow of [^{3}H] NE during basal (0.088 ± 0.018 10^{3} DPM/100 mg/min), ES (7.550 ± 1.413 10^{3} DPM/100 mg/m), or post-ES (0.349 ± 0.151 10^{3} DPM/100 mg/m) time periods.

Endotoxin did not alter the neuronal metabolite 3,4-dihydroxyphenylglycol in basal (1.47 ± 0.171 DPM/100 mg/m), ES (5.663 ± 0.781 10^{3} DPM/100 mg/m), or post-ES (4.178 ± 0.914 10^{3} DPM/100 mg/m) periods.

Endotoxin did not alter the remaining metabolites of NE, 3,4-dihydroxymandelic acid, O-methylated deaminated compounds, and normetanephrine during basal, ES or post-ES periods.

The concentration of [^{3}H] NE (15.929 ± 3.0118 10^{3} DPM/100 mg/m) or its metabolites in vein was not changed significantly by endotoxin.

The contractile tension developed in control vessels in response to ES (6.115 ± 0.881 g/100 mg) was not altered significantly by endotoxin.

Discussion: These data provide important insights into the adrenergic system alterations induced by sepsis. 1) Endotoxin does not directly alter release of total tritium or [^{3}H] NE overflow and thus the high systemic levels of NE and peripheral NE depletion observed in sepsis are not an effect of endotoxin induced release of NE.
2) Endotoxin does not alter normal neuronal and extraneuronal uptake and metabolism of [^{3}H] NE and thus endotoxin does not directly increase circulating NE or cause peripheral NE depletion by alterations in uptake or metabolism. 3) Endotoxin does not directly alter smooth muscle cells to either enhance or impair contractile responses. These conclusions assume that the endotoxin concentrations used and the time of exposure were adequate and that other variables were absent.

Supported by the Foundation for Anesthesia Education and Research with a grant from the Burroughs Wellcome Fund and US PHS grant GM41797.

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Title: THE CEREBRAL HEMODYNAMIC AND METABOLIC EFFECTS OF I-653 IN DOGS

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Introduction. I-653 is a new inhalation anesthetic that differs from isoflurane in the substitution of a fluorine for the chlorine on the α carbon of the ethyl group. This anesthetic has a low solubility (blood gas partition coefficient = 0.42) similar to that of nitrous oxide (0.47) resulting in very rapid induction of and emergence from anesthesia. Cardiovascular and EEG effects in swine[1,2] have been reported to be similar to those of isoflurane. The purpose of the present study was to evaluate the effects of 0.5-2.0 MAC I-653 on cerebral function as measured by EEG activity, cerebral metabolism (CMRO$_2$), cerebral blood flow (CBF), and intracranial pressure (ICP) in a dog model similar to that used previously for isoflurane.[3]

Methods. Following approval by the Animal Care and Use Committee, cerebral studies were done in 6 dogs. Anesthesia was induced with halothane and oxygen, and ventilation was controlled to maintain normocarbia. Halothane was discontinued and 1.5 MAC I-653 (11%) administered via a modified DM-5000 vaporizer. Cannulae were inserted into a femoral artery for blood sampling and pressure measurement, into a femoral vein for blood return from the cerebral blood flow measurement, and into the sagittal sinus for direct measurement of cerebral blood flow and CMRO$_2$. A fiberoptic intracranial pressure measurement device and a thermistor probe were inserted into the parietal epidural space. The MAC concentrations of I-653 were studied in random order. Each study period consisted of 10 min equilibration at the MAC level followed by 20 min of measurements. At each concentration measurements were taken at 5 min intervals for determination of heart rate (HR), mean arterial pressure (MAP), CBF, CMRO$_2$, ICP, cerebrovascular resistance (CVRI), and EEG. Arterial blood gases, blood glucose and lactate, and end-tidal I-653 were measured at 5 and 15 minutes. Additional measurements were taken at 1.5 and 2.0 MAC I-653 to demonstrate the effect of supporting the MAP with phenylephrine. At the end of the study, cerebral biopsies were taken for determination of the cerebral energy state by measuring levels of ATP, phosphocreatine, glucose, and lactate.

Results. I-653 produced a dose-dependent decrease in cerebral vascular resistance from 1.53 ± 0.21 $mmHg \cdot ml \cdot min^{-1} \cdot 100g^{-1}$ at 0.5 MAC to 0.50 ± 0.03 $mmHg \cdot ml \cdot min^{-1} \cdot 100g^{-1}$ at 2.0 MAC I-653. This was accompanied by an increase in CBF from 61 ± 7 $ml \cdot min^{-1} \cdot 100g^{-1}$ at 0.5 MAC to 78 ± 3 $ml \cdot min^{-1} \cdot 100g^{-1}$ at 1.5 MAC (Fig 1). With higher concentrations of I-653 (2.0 MAC), CBF decreased to 52 ± 5 $ml \cdot min^{-1} \cdot 100g^{-1}$ because of a decrease in MAP to 43 ± 2 mmHg if MAP was supported at 70 mmHg with phenylephrine. CBF increased to 87 ± 3 $ml \cdot min^{-1} \cdot 100g^{-1}$ indicating impairment of autoregulation at this concentration. EEG activity progressively decreased with increasing concentrations of I-653, but even at 2.0 MAC I-653 isoelectricity was not observed. Instead, a curious adaptation response, perhaps indicative of a more wakeful state, was observed within 20 min (Fig 2) of 2.0 MAC I-653. Accompanying the dose-related suppression of EEG activity, there was a dose-related decrease in CMRO$_2$ from 3.41 ± 0.20 $ml \cdot min^{-1} \cdot 100g^{-1}$ at 0.5 MAC to 2.43 ± 0.17 $ml \cdot min^{-1} \cdot 100g^{-1}$ at 2.0 MAC. An increase in CMRO$_2$ from 2.43 to 2.57 $ml \cdot min^{-1} \cdot 100g^{-1}$ accompanied the adaptation response observed on the EEG at 2.0 MAC I-653. Cerebral energy stores measured at the end of the study remained normal.

Discussion. I-653 is similar to other volatile anesthetics in that it is a potent cerebral vasodilator and autoregulation appears to be attenuated at higher concentrations. The dose-related reduction in CMRO$_2$ is similar in magnitude to that observed with isoflurane[3] and thiopental.[4] However, I-653 seems to be unique among the volatile anesthetics in that its dose-related suppression of neuronal function, as evidenced by EEG activity, and the accompanying decrease in CMRO$_2$ are limited by an adaptation response occurring at 2 MAC I-653.

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Figure 1

Effect of I-653 on Cerebral Blood Flow

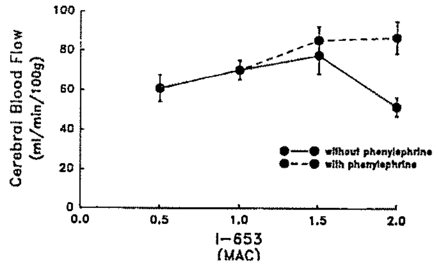
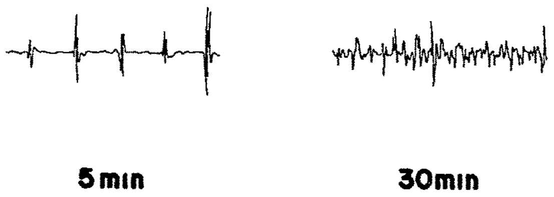


Figure 2



Adaptation Response
2.0 MAC

INFLUENCE OF INTRAVENOUS LIDOCAINE ON BRAINSTEM AND SOMATOSENSORY EVOKED POTENTIALS

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Introduction: Intravenous lidocaine infusion has been used as an adjunct to general anesthesia.[1] More recently, this technique has been used in treatment of chronic pain.[2] We have successfully utilized systemic lidocaine infusion as an anesthetic adjunct in several surgical procedures on the spinal cord where the need to monitor both motor and somatosensory evoked potential precluded the use of high dose inhaled anesthetic as well as neuromuscular blockade. However, the influence of lidocaine on somatosensory evoked potential (SSEP) has not been studied. In addition, the literature is conflicting on the influence of lidocaine on brainstem auditory evoked potential (BAEP).[3,4] Accordingly, we evaluated the influence of intravenous lidocaine on BAEP and SSEP in 4 healthy volunteers.

Method: The study was approved by the institutional human subjects review committee. Four healthy volunteers, aged 32-48, free of systemic disease, and all with normal hearing, were studied. BAEP and SSEP were recorded from scalp electrodes placed over the vertex and over the right parietal cortex. Additional electrodes were placed over the C7 spine and Erb's point to record the peripheral conduction. BAEP was recorded with reference to the ipsilateral ear lobe in response to alternate clicks set at 65 dB above the normal hearing level while SSEP was referenced to forehead and recorded in response to contralateral median nerve stimulation using a square wave current at 2 milliamp. above the motor threshold. A continuous intravenous infusion was started in the non-stimulated arm and a catheter inserted in the antecubital fossa of the stimulated arm for blood sampling purposes. Blood pressure, ECG and pulse oximetry were monitored continuously throughout the study. Following recording of baseline BAEP and SSEP, a 0.8% lidocaine infusion was commenced and a loading dose of 5 mg/kg was given over 30 minutes after which a maintenance dose of 45 ug/kg/min was given. The regimen is based on known pharmacokinetic data and aimed to achieve blood levels of 3-5 ug/ml. BAEP and SSEP recordings were repeated after commencement of maintenance infusion. Blood samples for lidocaine assay by gas chromatography were obtained immediately before and after completion of repeat BAEP and SSEP recordings. All evoked potential recordings were performed in duplicate to ensure reproducibility. Control recordings were compared with post-lidocaine infusion recordings using paired t-test, and a P value of less than 0.05 was considered statistically significant.

Results: All subjects were successfully studied. One subject experienced dysphoria and did not receive the full loading dose. Two subjects experienced drowsiness, accompanied by slurred speech in one, and perioral numbness in the other. No subject reported tinnitus. The lidocaine blood levels ranged from 2 to 5 ug/ml (mean of 3-4 ug/ml. Analysis of peaks V of BAEP and N20 (the cortical component of SSEP) revealed that neither latency nor amplitude was significantly affected by lidocaine at the blood level achieved. In the subject with the lowest blood level (2 ug/ml), the post-lidocaine recordings were virtually identical to control. In the subject with the highest blood level (5 ug/ml), the latency of peak V was slightly increased. The latency N20 was also slightly increased in this subject while the amplitude was unchanged. The data are summarized in Table I.

	BAEP		SSEP	
	PEAK V LAT. (msec) ±SE	PEAKV AMP. (µv) ±SE	N20 LAT (msec) ±SE	N20 AMP. (µv) ±SE
CONTROL	6.76 ±0.09	0.29 ±0.02	19.40 ±0.50	2.80 ±0.26
AFTER LIDOCAINE	6.90 ±0.13	0.24 ±0.01	20.08 ±0.58	3.00 ±0.19

Discussion: The local anesthetic action of lidocaine causing nerve conduction blockade indicates that this drug affect all excitable tissues. Its effects on the central nervous system are known to be multiphasic - at low doses, little or no effects are seen, at higher doses, central nervous system depression is seen, at toxic levels excitation is manifested by convulsive activity, at still higher doses, coma can occur. These observations are explained by the fact that lidocaine affect neurons in a differential manner, and the effects at any level are dependent on the interactions of the various effects of lidocaine on the different pathways. Because of these variable manifestations, the effect of lidocaine on BAEP and SSEP cannot be reliably predicted. Moreover, the reported observation of tinnitus with toxic doses of lidocaine suggests that lidocaine may have a direct effect on the auditory system. The results reported in the literature, however, are conflicting. Our results indicate that the influence of lidocaine on BAEP, in the therapeutic level of 2-5 ug/ml, is negligible. However, none of our subjects developed tinnitus. As well, there was a tendency for peak V latency to increases in the subjects with higher blood levels. Similarly, with SSEP, neither the amplitude nor the latency of N20 was significantly influenced by lidocaine although a small tendency for the latency as well as the amplitude to increase was observed. These changes, however, one so small that they are unlikely of any clinical significance. We conclude that therapeutic doses of lidocaine do not affect these short latency BAEP and SSEP and would not interfere with intraoperative monitoring.

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Title: HEMODILUTION ATTENUATES PRESSOR RESPONSES DURING PHENYLEPHRINE INFUSIONS IN DOGS

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Introduction. Cell-free solutions are being used increasingly for blood replacement to avoid the risks involved in autologous blood transfusions (1). Previous studies in anesthetized dogs have demonstrated that the resultant hemodilution decreases the responsiveness of the circulation to selective beta-adrenergic receptor stimulation with isoproterenol (2), but information is lacking on the effect of hemodilution on vascular responses to selective alpha-adrenergic receptor stimulation with, for example, phenylephrine. Such information may provide insight into the role of hemodilution in the reduced responsiveness to phenylephrine that is frequently observed clinically when this agent is used to treat hypotension in patients undergoing open-heart surgery in which crystalloids are utilized to prime the cardiopulmonary bypass circuit. The present study was performed to evaluate pressor responses to intravenous infusions of phenylephrine before and following isovolemic hemodilution.

Methods The study was conducted in compliance with our institution Animal Investigation Committee. Six heartworm-free, conditioned mongrel dogs were anesthetized with fentanyl (20 ug/kg i.v. initially with supplementation at 2 ug/kg/min). Neuromuscular blockade was accomplished with vecuronium. After tracheal intubation, the dogs were mechanically ventilated with FIO2 = 1.0 (PO2, 294 ±24 mmHg; PCO2, 36 ±1 mmHg; pH, 7.42 ±0.01). Polyethylene catheters were positioned in the thoracic aorta via a femoral artery to measure arterial blood pressure and into the vena cava via a femoral vein for intravenous infusions. Steady-state changes in mean arterial blood pressure were evaluated during graded, intravenous infusions of phenylephrine (range 0.7 - 5.6 ug/kg/min) before and following isovolemic hemodilution with 5 % dextran-40 (45 ml/kg body weight). Statistical analysis was performed with the Student's t test for paired samples.

Results. Before hemodilution, phenylephrine caused dose-dependent increases in mean arterial pressure from the control value of 109 ±14 mmHg (Figure 1). Hemodilution to an hematocrit of 17 ±3 % had no significant effect on baseline mean arterial pressure. However, as demonstrated in Figure 1, it attenuated pressor responses at each phenylephrine dose resulting in a rightward shift of the dose-response relationship.

Discussion. The present results indicate that hemodilution reduces the responsiveness of vascular alpha-adrenergic receptors to stimulation by phenylephrine. The mechanism for this finding is uncertain, although it may be related to antagonism by the local vasodilating effects of anemic hypoxia. Another possibility is that hemodilution itself activates peripheral alpha-adrenergic receptors reflexly, thus reducing the reserve available for further pharmacological activation.

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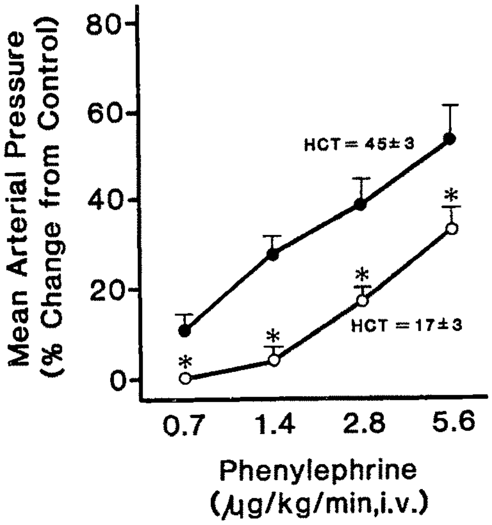

Figure 1. Pressor responses during graded infusions of phenylephrine before and following hemodilution. * P<0.05, from pre-hemodilution pressor response.

TITLE: POST CESAREAN SECTION ANALGESIA REQUESTS ARE INDEPENDENT OF WHEN EPIDURAL FENTANYL IS GIVEN

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Introduction. Epidural fentanyl is used to relieve post cesarean section pain (1,2). It has been suggested that lipid soluble local anesthetics increase the duration of epidurally administered morphine (3). The purpose of this study was to compare the duration of analgesia of epidural fentanyl on post cesarean section pain when mixed with lidocaine 2% plus epinephrine 1:200,000 and administered during initiation of the epidural anestheisa or when administered with normal saline at the end of surgery.

Methods. The protocol was approved by the Institutional Review Board and informed consent was obtained in all patients. Fourteen ASA Class I or II patients scheduled for elective cesarean section who had requested epidural analgesia were randomly assigned to two groups. Group I patients (n=7) received fentanyl 1 mcg/kg mixed with lidocaine 2% plus epinephrine 1:200,000 during the institution of epidural anesthesia. Group II patients (n=7) received epidural fentanyl 1 mcg/kg mixed in 10cc preservative free normal saline at the end of surgery during skin closure. An epidural catheter was placed at L2-3 or L3-4 interspace. Anesthesia up to T4 level was obtained in all cases by giving increments of lidocaine 2% plus epinephrine 1:200,000. Intraoperative patient discomfort was assessed by anesthesiologist using a four category rank scale (none, mild, mod, severe) during skin incision, bladder retractin, delivery, uterine and peritoneal closure.

At the end of surgery and every 30 minutes thereafter the sensory level of anesthesia and a linear visual analog pain score were obtained by a blinded observer. Respiratory rate, pulse rate, and blood pressure of all patients were recorded.

The time to regression of sensory anesthesia to T12 (T12) and first supplemental narcotic (N) request was noted. The duration of opioid analgesia was defined as the difference between the time of regression of sensory anesthesia to T12 and the time to patient request for narcotic analgesia (N-T12). If a patient requested narcotic analgesia before the sensory block regressed to T12, an N-T12 score of zero was assigned. Difference in mean duration of opioid analgesia between two groups were assessed using students t-test for unpaired data.

Results. Mean age, height, and weight of the patients were not significantly different in the two groups. Table 1 shows the duration of opioid analgesia in Group I and Group II. The mean duration of opioid analgesia when fentanyl was mixed with lidocaine 2% plus epinephrine 1:200,000 and given during the establishment of the epidural block (29±62 min) was not significantly different from the duration of analgesia when fentanyl was mixed with normal saline and given at the end of surgery (32±56 min). Interestingly only three of the seven patients in each group had opioid analgesia scores greater than zero. On the contrary, the quality of intraoperative analgesia as assessed subjectively by the anesthesiologists was superior when fentanyl was given with lidocaine (fig. 1).

Discussion. Under conditions of this study epidural fentanyl (1mcg/kg) did not provide significant pain relief following cesarean delivery. There was no difference in the duration of opioid analgesia when fentanyl was administered mixed with lidocaine 2% plus epinephrine 1:200,000 at the establishment of the block or when fentanyl mixed with normal saline was administered at the end of surgery. However, synergism between fentanyl and lidocaine when given together was evidenced by the intraoperative comfort of patients. The short duration of epidural fentanyl analgesia requires that fentanyl be given by repeated injections or by continuous infusion for effective pain relief following cesarean delivery.

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Table 1. Patient characteristics*

	Group I (n=7)	Group II (n=7)
Age (yrs)	26.6±8.2	28±7.5
Weight (kg)	99.5±22.6	92.3±22.9
Height (cm)	163±7.2	161±7.6
Duration of opioid analgesia (min) (N-T12)	29±62	32±56

*Values are expressed as mean ±SD.

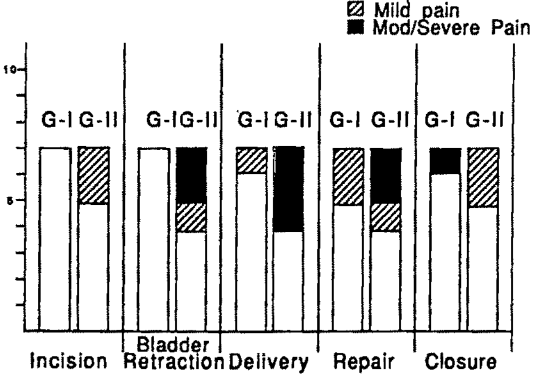

Fig 1. The incidence of intraoperative discomfort

TITLE : PROPOFOL REQUIREMENTS FOR INDUCTION OF ANESTHESIA IN UNPREMEDICATED CHILDREN

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Introduction: Propofol is a useful intravenous anesthetic agent for day care surgical patients because of its lack of side effects and rapid recovery. In an earlier study we compared the characteristics of propofol with thiopentone in unpremedicated children[1]; it was found that Propofol caused an unacceptably high incidence of serious pain on injection (20%) and that the dose 2,5 mg/kg bodyweight (BW) needed further evaluation.

The present randomized study was undertaken to determine the appropriate induction dose of propofol and to limit the pain on injection in unpremedicated children undergoing day-care surgery.

Methods: Approval of the Human Research Committee and informed parental consent were obtained.

90 ASA PS 1 children were divided in 3 age groups of 30 children each: 3-6 yr, 6-10 and 10-16 yr, randomly allocated to 3 dose groups : 2.5, 3.0 or 3.5 mg/kg BW.

No premedication was administered. On arrival in the induction room baseline measurements of blood pressure, heart rate, respiratory rate and non-invasive O_2 saturation (Biox 3700) were taken. Intravenous access was established, usually in the dorsum of the hand using a 22G or 20G cannula. To prevent pain on injection 5 mcg/kg BW alfentanil was administered 20 seconds prior to the administration of the allocated dose of propofol.

During the induction, pain or excitatory reactions were noted. Eyelash and mask reflex as well as the cardiorespiratory parameters were observed at 30, 60, 120, 180 and 300 seconds. Ventilation was controled if apnea lasted more than 1 minute or caused the O_2 saturation to drop below 90%. Anesthesia was maintained with 66% N_2O in O_2 by mask during this period. All objective measurements and observations were made by an independent observer. Data were analyzed using Student's T-test, Chi-square analysis and analysis of variance where appropriate. $P < 0.05$ was considered significant.

Results: Age, weight and gender distribution of the patients were similar in the 3 dose groups; there were 67 boys and 23 girls, the imbalance being due to the type of surgery performed. Severe pain was present in 3 (3%) patients. Excitatory effects were seen in 15 cases (17%); no statistical significance was noted between the 3 dose or age groups. One patient had a positive eye lash reflex. One patient showed a positive mask reflex. No bradycardia or clinically significant hypotension was observed. Cardiovascular parameters showed a significant reduction from the preoperative values ($P < 0.05$) but no significance was shown between the age or dose groups. Short term ventilatory control was needed in 21 patients (24%), which is comparable to the 23% found in the previous study without alfentanil; ventilatory control was more frequently needed in the 10-16 year age group ($P < 0.01$), but this was independent of the dose.

Conclusion: Our study showed that all patients receiving 3.0 and 3.5 mg/kg BW propofol, preceded by alfentanil 5 mcg/kg BW were asleep. Two patients not asleep were in the oldest age - and in the 2.5 mg dose group. Addition of alfentanil prior to the use of propofol decreased the incidence of severe pain without influencing the cardiovascular and respiratory parameters.

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A comparison of propofol with thiopentone for induction of anesthesia in unpremedicated chilren. Anesthesiology 1988; 69: A741.

TITLE: AUTOTRANSFUSION OF MEDIASTINAL SHED BLOOD: HEMATOLOGIC EFFECTS

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INTRODUCTION: The purpose of this study was to characterize the coagulation profile of mediastinal shed blood (MSB) using new specific hemostasis markers and to assess the role of autotransfusion in postoperative bleeding following cardiac surgery.

METHODS: The use of human subjects was approved by the hospital research committee and informed consent was obtained from all patients. Twenty patients who underwent cardiac operations on extracorporeal bypass were studied. MSB was collected using the Sorenson Receptal ATS System (Sorenson Research Corp., Salt Lake City, Utah). Samples were taken of MSB after 40 micron filtration before autotransfusion. Patient samples were drawn post-op immediately on arrival to the SICU and 15 minutes following transfusion of MSB. Data was analyzed using a paired t-test. Fibrinopeptide A (FPA) and D-dimer (DDi) were analyzed by ELISA. Fibrinogen degradation products (FD) were measured using latex agglutination methods. Antithrombin III (ATIII) and alpha 2- antiplasmin (alpha 2-AP) were measured using chromogenic technology on an automated analyzer.

RESULTS: MSB contained very high levels of fibrinopeptide A, fibrinogen degradation products and D-dimer. Patient levels of these markers were elevated following autotransfusion (Table A). Antithrombin III and alpha 2- antiplasmin levels were low in MSB. These markers did not change in patients following autotransfusion (Table B).

DISCUSSION: It has been suggested that massive autotransfusion of MSB may contribute to development of hemorrhagic disorders.[1] The elevation of coagulation and fibrinolysis activation markers such as fibrinopeptide A, fibrinogen degradation product and D-dimer found in MSB and in patient plasma post-transfusion suggest fibrin formation and degradation were accelerated. The low levels of the coagulation inhibitor antithrombin III and the fibrinolysis inhibitor alpha 2- antiplasmin in MSB suggest a high concentration of activated thrombin and plasmin. In an earlier study, we showed MSB has elevated levels of the platelet released proteins platelet factor 4 and beta-thromboglobulin suggesting platelet activation is occurring.[2] Therefore, large volumes of transfused MSB may possibly contribute to the development of disseminated intravascular coagulation in the postoperative period.

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TABLE A

	FPA (0-3ng/ml)	FDP (≤10ng/ml)	D-dimer (≤200ug/ml)
MSB	7693±826	467.2±340.6	108726±32317
Patient Pre-MSB	42.6±55.3	24.0±10.7	2383±1210
Patient Post-MSB	154.4±246.2*	160.0±215.8*	10110±3120*

* = significant at $p \leq .05$

TABLE B

	ATIII (75-120%)	alpha 2-AP (75-120%)
MSB	22.1±7.6	20.4±12.4
Patient Pre-MSB	53.4±14.8	66.4±11.7
Patient Post-MSB	58.5±12.6	65.2±11.3

Title: IS BICARBONATE DETRIMENTAL IN THE TREATMENT OF MILD TO MODERATE METABOLIC ACIDOSIS?

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Introduction: The efficacy of NaHCO3 therapy in the treatment of metabolic acidosis has been questioned in recent years. Canine studies of severe metabolic acidosis have found that NaHCO3 infusion resulted in decreased cardiac output (CO), decreased blood pressure (BP), decreased pH, increased lactate production, and decreased tissue oxygen consumption (1,2,3,4). More recently, in patients (pts) with congestive heart failure without acidosis, 3/10 developed myocardial lactate production following NaHCO3 infusion, suggesting that NaHCO3 may precipitate myocardial ischemia (5). However, other human data are limited. In order to determine the effects of NaHCO3 on hemodynamics, myocardial ischemia, and metabolic parameters, we studied patients with metabolic acidosis during surgery who were randomized to receive NaHCO3 or saline.

Methods: This study was approved by the Human Research Committee at our institution and all subjects gave informed consent prior to study. We prospectively studied 22 pts at risk for coronary artery disease (CAD), undergoing major surgery (11 CABG-all studied post-bypass, 4 aortic bypass, 4 radical prostatectomy, 1 adrenal mass, 1 renal mass, 1 ORIF hip). If a pt developed a base deficit between 3 and 12 mEq/L (mean= 4.8) he was randomized to one of two treatment groups: a) NaHCO3 group- received NaHCO3 (0.86 mEq/cc) by IV bolus (over < 1 minute) in the amount (0.2)(body weight in kg)(base deficit) mEq up to a maximum of 88 mEq (mean treatment =62 mEq); b) Control group- received NaCl (0.86 mEq/cc) in a similar amount by IV bolus (mean= 75 mEq). Continuous data collected from 5 minutes before treatment to 20 minutes after included: BP, heart rate (HR), pulmonary artery (PA) pressures when available, transesophageal echocardiography (TEE), and ECG by Holter monitor. Discrete data were collected at baseline (within 5 minutes prior to treatment) and at 5 and 20 minutes after treatment and included: arterial blood gases (ABG), lactate levels, and mixed venous gases, CO, and pulmonary capillary wedge pressure (PCWP) when a PA line was in place. Myocardial ischemia was measured by ST-segment changes on Holter ECG continuously and by new segmental wall motion abnormalities (SWMA) on TEE at 5 minutes before treatment and after treatment at 1, 3, 5, 10, 15, and 20 minutes. Differences between variables were compared using t-test.

Results: 1/8 pts in the NaHCO3 group developed both ECG ischemia (8 minutes after treatment) and new SWMA on TEE (occurred 1 minute after treatment and resolved at 10 minutes after). 1/8 pts in the NaCl group developed ECG ischemia (15 minutes after treatment), and another one developed a new SWMA on TEE (15 minutes after treatment). The hemodynamics (BP, HR, PA) were not significantly different before and after treatment in either group (out to 20 minutes). See Table 1. The CO also did not change significantly with either treatment, but did tend to increase in the NaHCO3 group at 5 minutes after treatment (average increase of 1.5 L/min). No significant change occurred in the PCWP in either group. The pH rose significantly in the NaHCO3 group after treatment (mean= 7.38 to 7.41, p=.02) but did not change in the NaCl group. The arterial pO2 decreased significantly in the NaHCO3 group over 20 minutes (mean= 368 to 306 mmHg, p=.02), with no change in the NaCl group. The lactate production 5 minutes after treatment tended to increase more in the NaHCO3 group (514 uM/min) than in the NaCl group (164 uM/min) (normal lactate production is 1390 uM/min). The total body oxygen consumption did not change significantly in either group.

Table 1. Hemodynamic variables (mean ± SD)

TIME	SBP-Bi	SBP-NaCl	HR-Bi	HR-NaCl
- 5	122±27	106±20	75±17	88±22
0	123±25	120±19	79±19	89±21
1	121±28	108±20	77±16	88±24
3	129±23	112±22	78±14	89±22
5	128±32	120±33	78±14	89±19
10	122±18	115±18	78±15	92±23
15	123±29	113±13	78±17	89±23
20	121±21	119±19	78±17	91±21

TIME	CO-Bi	CO-NaCl	PCWP-Bi	PCWP-NaCl
- 5	4.7±1.7	6.8±1.2	11±3.2	16±3.1
5	6.2±2.0	7.0±1.6	13±4.7	12±5.5
20	4.9±2.2	6.8±2.5	14±3.8	12±5.9

Discussion: In contrast to results in severely acidotic animals and humans with congestive heart failure (1,2,3,4,5), these data suggest that treatment of mild to moderate metabolic acidosis with NaHCO3 by IV bolus in pts at risk for CAD does not result in adverse hemodynamic changes, increased incidence of ischemia, or decreased total body oxygen consumption. However, NaHCO3 treatment was associated with a decrease in arterial pO2, but this may not be clinically significant since the pts all remained well oxygenated and no hemodynamic deterioration or increased incidence of myocardial ischemia occurred. In addition NaHCO3 did tend to increase lactate production. Further investigation is needed to determine the significance of these metabolic effects.

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SEVERE BRADYCARDIA WITH PERCUTANEOUS TRIGEMINAL GANGLION COMPRESSION: ANESTHETIC APPROACH

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Introduction

Percutaneous trigeminal ganglion compression (PTGC) was introduced in 1983 by Mullan and Lichtor (1). Compared to rhizotomy, PTGC does not cause intraoperative patient discomfort since it can be performed under general anesthesia, and the incidence of corneal reflex impairment or severe hypesthesia is much lower (2). At our Institution, Brown demonstrated that PTGC is associated with bradycardia in 70% of the cases and hypotension in 55% of the cases when the tip of the needle enters the foramen ovale or upon balloon advancement or inflation (3). Previous reports by Mullan and Lichtor identified bradycardia of short duration (1). Belber and Rak observed cardiac arrest in one patient (4). Blocking this trigeminal depressor response with preoperative anticholinergic agents has the potential disadvantage of abolishing clinically useful indications of correct needle/balloon placement by the surgeon (2). The purpose of this report is to present a safe and effective anesthetic protocol for this procedure while keeping the trigeminal depressor response intact.

Methods

Anesthetic and operative records of twenty-seven patients having PTGC between January 1987 and July 1989 were reviewed, following approval from the Institutional Review Board. A standard protocol was followed, consisting of: no anticholinergic agent for premedication, intraoperative monitoring of ECG, arterial blood pressure (18 invasively), pulse oximetry, capnometry, and esophageal temperature. Anesthesia was induced with thiamylal, then maintained with isoflurane, nitrous oxide, and oxygen. Some patients also received incremental doses of sufentanil. Atracurium or vecuronium was used for muscle relaxation. In all cases ventilation was controlled. Prior to induction, each patient was connected to a non-invasive VVI demand pacemaker (ZMI, Model NTP-3003). After induction of anesthesia, the external pacemaker was tested and a demand heart rate of 45, 50, or 60 was set depending on the post-induction heart rate. Atropine was also readily available.

Results

Cardiovascular effects observed included bradycardia, tachycardia, hypotension, and hypertension. Bradycardia occurred most frequently and seven patients had bradycardia significant enough to activate the external pacemaker. There were 3 males and 4 females, ranging in age from 41 to 92 years. The mean age was 66 years. Four patients were ASA II and 3 were ASA III. The 7 patients reviewed showed clinical bradycardia or asystole with needle insertion or balloon inflation. Two patients became briefly asystolic and were treated by external pacing and subsequent balloon deflation. One of these patients was treated with atropine following external pacing when repeated balloon inflation resulted in a second episode of asystole. The remaining 5 patients had bradycardia, with reduction of heart rates ranging from 34 to 42 percent below post-induction heart rates (see Table 1). In each case, the bradycardia responded to treatment with external pacing, and anticholinergic agents were not required. After balloon deflation, the heart rates returned to near post-induction levels.

TABLE 1

Heart Rate Changes During
Percutaneous Trigeminal Ganglion Compression

Patient	Pre-Induction	Post-Induction	PTGC	Post PTGC
1	84	56	0 (100)	70
2	82	64	0 (100)	76
3	72	50	29 (42)	52
4	76	56	37 (34)	72
5	84	76	45 (41)	78
6	80	80	50 (38)	100
7	90	94	60 (36)	94

In parentheses, percent decrease from post-induction heart rate.

Discussion

The trigeminal depressor response (TDR) during PTGC can be expected to result in clinically significant bradycardia and hypotension (3). In our experience, brief asystole occurred in 2 patients. Severe bradycardia and asystole were treated successfully in all cases with the external pacemaker.

We conclude that bradycardia and asystole associated with stimulation of the TDR during PTGC can be successfully treated with a transcutaneous demand pacemaker. Avoidance of anticholinergic agents preoperatively and prior to balloon inflation, keeping the TDR intact, enables the surgeon to more easily identify correct needle/balloon placement. Adequate monitoring and placement of the external pacemaker prior to induction are essential to rapid and effective treatment of these potentially life-threatening responses.

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TITLE:

ISOFLURANE ATTENUATES THE SYMPATHETIC REFLEX RESPONSE OF *IN SITU* MESENTERIC VEINS IN THE RABBIT

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Introduction: The influence of Isoflurane (ISO) has been examined in relation to regional blood flows, cardiac output, afferent and efferent sympathetic pathways, and intracellular membrane currents,[1] but little is known about the effect of ISO on the reflex control of splanchnic venous capacitance. Recent studies have demonstrated that mesenteric veins actively constrict and dilate in response to baroreflex changes.[2] The purpose of this study is to examine the effects of ISO on sympathetically mediated changes in the reflex response of small mesenteric veins (500-1000μm).

Methods: After Institutional Animal Care Committee Approval, seventeen New Zealand white rabbits (1-2 kg) were anesthetized with thiamylal (25mg/kg) and maintained with a constant infusion of alpha-chloralose (15mg/kg/hr). Surgical preparation included tracheotomy, cannulation of the femoral artery and vein, and a 5 cm laparotomy. The carotid arteries were isolated bilaterally for occlusion (BCO), and the aortic nerves were dissected and sectioned for electrical stimulation (ANS, .05-.10 mA, 20 Hz/10 sec). In seven rabbits, silver electrodes were fixed to the celiac ganglion for stimulation (CGS, 3-5 mA, 5, 10, 20 Hz/2 min). A 13 cm loop of terminal ileum was exteriorized and mounted in a superfusion chamber continuously supplied with physiological salt solution (PSS) at 37° C. Portions of free-running mesenteric veins were fixed to a silgel bed with 75μm pins. Continuous measurements of vein diameter (VD) were obtained with an on-line video micrometer system. Simultaneously, venous pressure (VP) was monitored at the same site using a servo-null micropipette pressure measuring system. In nine rabbits, 0.75 and 1.5% inhaled ISO were administered in randomized order resulting in blood levels of 0.54 and 0.88 mM, respectively. In eight additional rabbits, PSS equilibrated with 4% ISO (1.02 mM) was administered directly to the mesenteric superfusate.

Results: *ANS and BCO.* Venodilation in response to ANS was attenuated by 1.5% inhaled ISO, whereas venoconstriction in response to BCO was suppressed by both 0.75 and 1.5% inhaled ISO. VP increases during BCO and decreases during ANS were also attenuated by inhaled ISO.

Inhaled ISO	0%	1.5%	0%	0.75%
ANS (n=8)				
Baseline VD (μm)	675±35	720±43*	658±33	693±44
ΔVD (μm)	20±3	1±.7*	19±1	15±4
%Δ	3.1±.4	.2±.1*	2.7±.2	2.3±.6
Baseline VP (mmHg)	8.1±.2	7.7±.5	8.6±.3	7.9±.4
ΔVP (mmHg)	-.3±.1	0.0±0*	-.3±.1	-.3±.1
%Δ	-3.7±1.3	0.0±0*	-3.9±1.8	-3.2±1.6
BCO (n=7)				
Baseline VD (μm)	681±30	718±42	680±25	704±28
ΔVD (μm)	-26±3	.3±3*	-32±9	-3±2*
%Δ	-3.9±.5	.1±.4*	-4.7±1.5	-.5±.3*
Baseline VP (mmHg)	8.1±2	7.7±.4	8.5±.4	7.4±.5
ΔVP (mmHg)	.8±.2	.3±.2*	1.0±.2	.3±.2*
%Δ	10.3±2.2	3.8±1.7*	12.6±1.3	4.3±1.9*

*p<.05 compared to 0% ISO.

There was a tendency towards venodilation in the presence of inhaled ISO alone before BCO or ANS. The inverse relationship between VP changes and VD changes in the absence of ISO demonstrates that these were active responses to reflex stimuli.

CGS. Increases in the frequency of CGS stimulation produced corresponding increases in venoconstriction at significant levels compared to baseline VD. Active venoconstriction in response to CGS was not suppressed by administration of 4% ISO equilibrated in the PSS superfusate.

Superfused ISO	Pre-ISO	ISO	Post-ISO
CGS (n=6)			
Baseline VD (μm)	667±45	695±60	669±58
ΔVD at 5Hz (μm)	-58±9*	-31±5*	-41±9*
ΔVD at 10Hz (μm)	-95±16*	-63±6*	-60±10*
ΔVD at 20Hz (μm)	-111±23*	-92±19*	-80±13*

*p<.05 compared to baseline VD.

In two additional rabbits, 1.5% inhaled ISO did not suppress the response to CGS. In one additional rabbit, ISO administered in the superfusate did not inhibit venoconstriction in response to BCO.

Discussion: Inhaled ISO significantly suppressed the sympathetically mediated reflex responses of mesenteric veins. These direct observations of changes in venous reflexes support other reported findings of the suppressive effects of ISO on the baroreflex control of the total systemic vascular capacitance.[3] In our study, ISO induced changes were dose-dependent in response to depressor stimulus (ANS), while venoconstriction in response to pressor stimulation (BCO) was abolished even at the low dose. The protective effect of 0.75% inhaled ISO on the depressor response to ANS may be due to the association between reflex mediated sympathetic withdrawal and the anesthetic suppression of sympathetic tone.

The suppressive effects were not observed when ISO was administered locally to the vein at concentrations of superfused ISO similar to inhaled concentrations. Indeed, frequency dependent venoconstriction in response to CGS was preserved in the presence of superfused ISO. These results suggest that mediation of the suppressive effects of ISO on the reflex control of splanchnic venous capacitance may be central in origin.

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TITLE: *A PROSPECTIVE STUDY TO IDENTIFY THE FEATURES ASSOCIATED WITH DIFFICULTY AT LARYNGOSCOPY AND INTUBATION IN THE OBESE PATIENT*

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INTRODUCTION: One of the major problems in the anesthetic management of the obese patient is the safe securement of the airway. Technical difficulties may arise due to the presence of a short, thick neck, presternal and posterior cervical fat pads and a large tongue. Mallampati et al were able to reliably predict the chances of difficulty at laryngoscopy and intubation, in a population with normal weight, based on the preoeperative ability to visualize the pharyngeal structures (1). The usefulness of the Mallampati classification in predicting difficulty at intubation in the obese population has not been assessed. Adding to these technical problems are the physiological changes in the respiratory system, namely air trapping and reduction in functional residual capacity, which cause delay in nitrogen wash-out, prolong the time for adequate preoxygenation and result in more rapid desaturation. There has not been any study assessing the features in the obese patient that would help predict those who will desaturate rapidly. The aim of this study is to assess those features in the obese that would help in predicting technical difficulties at laryngoscopy and intubation and also those associated with rapid desaturation.

PATIENTS AND METHODS: Following approval by the Institutional Review Board, forty obese patients presenting for anesthesia and surgery requiring tracheal intubation were studied. Patients with airway problems unrelated to their obesity and patients with any cardiovascular, pulmonary, neurological, or hematological disease were excluded. All patients were assessed prior to induction by one of the investigators. The airway was classified after Mallampati. Measurements were taken of the patient's girth and chest. A clinical assessment of the distribution of adipose tissue was made. Standard monitors were applied. Oxygen saturation was measured using the fingertip pulse oximeter in the rapid update mode. The patients were preoxygenated with 100% oxygen at a flow rate of 101/min through a circle system with an in-line mass spectrometer until the expired nitrogen is less than 4% or until four minutes had elapsed. Anesthesia was induced with thiopental 4 mg/kg IV and suxamethonium 1 mg/kg was given for intubation. The time taken from injection of suxamethonium until desaturation to 95% on the pulse oximeter was recorded. The Mallampati grade at laryngoscopy was recorded and the reason for any difficulty at laryngoscopy was documented. Statistical significance was assessed using the Spearman rank correlation and the Chi2 test.

RESULTS: The patients in this study were aged between 20 and 58 years. There were 35 female and 5 male patients. Twenty-eight patients were between 30 and 100% over ideal body weight and twelve patients were between 100 and 180% over ideal body weight. The airway assessment results are displayed in Table 1. The time to desaturation to 95% was measured in twenty-six patients. Nine patients desaturated within 60-120 seconds and seventeen patients desaturated within 120-240 seconds. When time to desaturation was correlated with the parameters measured preinduction, there was a significant correlation with the % over ideal body weight (r = -0.49) and a closer correlation with the abdominal girth (r = -0.62).

DISCUSSION: Of the ten patients in Mallampati class 3, only one patient proved to be a difficult intubation. Difficulty in visualizing the glottis was mainly due to the presence of a large tongue, so the use of a tongue depressor in these patients might improve the predictability of this classification in the obese patient. Desaturation would be expected to correlate with increasing weight as FRC values fall below closing volume with increasing obesity. (2) The closer correlation of desaturation with increasing abdominal girth reflects the effect of the abdominal mass on FRC which would be exaggerated in the recumbent position that was used for intubation in this study. In this group of obese and morbidly obese patients, the criteria frequently used to predict difficulty of intubation in patients of normal weight were not of value. The more overweight the patient, the more likely he is to desaturate early, particularly if this excess weight is associated with a large abdominal girth.

TABLE 1

	Grade 1 glottis fully exposed	Grade 2 ant.commisure not visualiz.	Grade 3 only cornic. cartilage seen	Grade 4 corniculates not seen
CLASS 1 Uvula visualized n=26	25	1	0	0
CLASS 2 Uvula masked n=4	2	0	0	0
CLASS 3 Soft palate only n=10	9	0	0	1

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TITLE: THE EFFECT OF GASTRIC INTUBATION AND REMOVAL OF GASTRIC CONTENTS ON THE INCIDENCE OF POSTOPERATIVE NAUSEA AND VOMITING

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INTRODUCTION: Induction of anesthesia and tracheal intubation is often preceded by mask ventilation, which causes distention of the stomach. The gastric bubble may be further enlarged by the use of nitrous oxide.[1] These factors may have a significant influence on the incidence of postoperative nausea and vomiting. Insertion of a gastric tube and removal of the gastric contents may help reduce the incidence of these sequelae. Alternatively, the presence of a gastric tube, by pharyngeal irritation, may also contribute to postoperative nausea and vomiting. The effect of inserting a gastric tube and removing the stomach contents on the incidence of postoperative nausea and vomiting has not previously been investigated in similar groups of patients undergoing the same operative procedure.

METHODS: With the approval of the Institutional Review Board, thirty six consecutive patients, ASA 1 and 2, presenting for laparascopic tubal ligation, as day surgery patients, were investigated. Obese patients, patient with hiatus hernia or peptic ulcer disease or any patient with an airway problem that would preclude mask ventilation as the appropriate anesthetic technique, were excluded. The patients were randomly assigned to one of two groups. Group 1, 20 patients, had an orogastric tube inserted after induction of anesthesia and tracheal intubation. Gastric contents were removed and the tube was withdrawn prior to extubation. The ease of insertion of the gastric tube was assessed and confirmation of endogastric placement was determined by assessing pH of the aspirate. Group 2, 16 patients, did not have a gastric tube inserted.

Both groups of patients received the same anesthetic agents. Patients were premedicated with Bicitra 15 mls p.o. Induction of anesthesia was with thiopental 4 mg/kg and sufentanil 0.15 mcg/kg i.v. Muscle relaxation was achieved with vecuronium 0.1 mg/lg i.v. Patients were ventilated by mask with nitrous oxide in oxygen and intubated when adequately paralyzed. Anesthesia was maintained with nitrous oxide in oxygen and isoflurane (end-tidal 0.5-0.8%). Sufentanil and vecuronium supplements were given as required. The duration of surgery and anesthesia was recorded. The patients were assessed for the presence of nausea and vomiting by a blind observer, from the time of extubation until two hours postoperatively. Statistical analysis of the results was by the log likelihood chi2 test.

RESULTS:

Details of Patients Studied

	Group 1 n=20 (mean +/- SD)	Group 2 n=16 (mean +/- SD)
Duration of Surgery (mins)	41 +/- 14	35 +/- 7
Duration of Anesthesia (mins)	75 +/- 22	74 +/- 11
Dose of Sufentanil (mcg/kg)	0.08 +/- 0.04	0.15 +/- 0.02

The overall incidence of nausea and vomiting in this study was 28%. One out of 20 patients in group 1 (4%) was nauseated and no patient in this group vomited. Nine out of 16 patients in group 2 (56%) vomited. The difference was significant to a p value of <0.008.

DISCUSSION: The incidence of post-operative nausea and vomiting is influenced by the patients sex, site of surgery, duration of surgery and anesthesia, and the surgical technique.[2] The two groups of patients in this study were similar in all these aspects. The high incidence of vomiting of 26% may reflect the female population studied and the type of surgery performed. On the basis of the findings from this study, patients undergoing laparascopic surgery, using this anesthetic technique, will have a significantly lower incidence of postoperative vomiting if an orogastric tube is inserted and the gastric contents removed.

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TITLE: WILL AUTOMATED ANESTHESIA RECORDKEEPING WORK IN A LARGE UNIVERSITY HOSPITAL SETTING?

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Introduction.

In the late 1970's, several chairmen of departments of anesthesiology embarked upon ambitious projects: the replacement of the man-made anesthetic record with an automated record in all their operating rooms. Most of these early systems were installed in only one or two rooms, although one university had an installation in ten rooms.

The systems at these institutions were fraught with problems. Almost all were abandoned within a few years. There are several reasons for these failures.

Any large university hospital will be a difficult proving ground for new technology that must come into widespread use. Operating rooms are sometimes old and small. Residents rotate among several hospitals and turn over every three or four years. Faculty, CRNA's, students, and technical personnel must all learn to operate the equipment. In order for a piece of equipment to be powerful, it necessarily must be complex. Striking the balance between features and simplicity is always a challenge for designers.

University hospitals abound with skeptics. Anything new, anything unproven, anything that works less than perfectly the first day, will forever be suspect. Automated records also brought the fear of "Big Brother." The recordkeepers were as large as an anesthesia machine and were difficult to place satisfactorily in small operating rooms. Time was required to enter data, and it was especially difficult to keep both a manual record and a computerized record.

Methods.

With full knowledge of the minor successes and major failures of prior systems, Diatek Corporation embarked upon a five-year project in 1982: the development of the Arkive Patient Information Management System. The result was a console designed to fit around the anesthesia machine, with a plasma display which doubled as a touch screen for data entry. Voice entry of data was optional. The unit was entirely independent and self-contained, with the record printed right in the operating room.

Results.

The Arkive was formally placed on the market in October 1987. The first Arkive arrived at this large university hospital a month later, but it was kept hidden until several units were ready for installation. After prior experience with gossip about problems, and based upon prior failures to educate users in group settings, we introduced the Arkives in the first two rooms on ten minutes' notice one morning in May 1988. One-on-one teaching acquainted each new user in turn. Over 50 people learned to operate the system and more than 10 completed voice training. Software revisions, new features, and more Arkives were added until, on February 27, 1989, the Arkives became operational in all sixteen general operating rooms. The Arkive printed anesthetic record is now the official anesthetic record and hand-kept records need no longer be kept. User acceptance has grown slowly, but with a full-time Arkive consultant during weekdays and with someone available 24 hours a day on call, questions have been answered and problems have been solved. Help and trouble calls average approximately 20 per week. Paper jams and accidental unplugging (with eventual battery discharge) are the most frequent system problems. The Arkives are used in over 95% of all cases in these operating rooms. Over 2000 anesthetic cases have been compiled into a large database.

Discussion.

As a Beta test site, this university has had a unique opportunity to contribute suggestions for future revisions of the Arkive. Networking, a fully searchable database of thousands of cases, and improved entry of IV infusions await the near future.

Our suggestions for those who are considering the installation of automatic anesthesia recordkeepers include the following: (1) Install the system in all rooms, not some of the rooms. (2) Do not require that users keep both a manual record and an automatic record. (3) Train users on a one-on-one basis only. (4) Have someone on call for questions and problems 24 hours a day, 365 days a year. Under these circumstances automatic recordkeeping will likely be successful.

TRANSDERMAL FENTANYL FOR POSTOPERATIVE PAIN FOLLOWING LOWER ABDOMINAL SURGERY

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Introduction - Inadequate pain relief is a frequent post-surgical complaint and is in part due to the fluctuating serum opioid concentration which results from conventional intramuscular dosing. A new non-invasive device placed on the skin employs a reservoir containing a concentrated opioid. The opioid is released slowly via a rate-controlling membrane with drug made continuously available through transdermal absorption. This device, known as the Transdermal Therapeutic System, TTS (fentanyl)-50, is thin, (0.2 mm), 20 cm^2, multi-layered and is adhesive when applied to intact skin releasing approximately 50 ug/hr fentanyl. This abstract reports data from a double-blind, placebo-controlled study to determine the safety and efficacy of the TTS device in relieving postoperative pain in females recovering from lower abdominal surgery.

Methods - Fifty-four female patients between the ages of 26 and 61 years undergoing elective, lower abdominal surgery were enrolled in the study. All patients gave written informed consent to a protocol approved by the Institutional Review Board of the University of Texas Medical Branch, Galveston. Patients were randomly allocated to receive either TTS (fentanyl)-50, or a TTS (placebo). Transdermal systems were applied to the upper chest two hours before induction of general anesthesia (at the same time patients received 10 mg diazepam orally) and removed 24 hours later. Anesthesia was induced with fentanyl (100 ug, IV) and thiopental (4 mg/kg, IV) and maintained with O_2, N_2O, and isoflurane. No other opioids were administered intraoperatively. Muscle relaxants were administered as required.

For the first two hours following arrival in the PACU, all patients received morphine 2 mg, IV, q 5-10 minutes prn pain. Subsequently, patients received morphine, 5 mg IM, q 2 hrs, prn pain. Safety of the TTS device was assessed by hourly determination of vital signs, pain, sedation level, respiratory rate and oxygenation (via pulse oximetry) for 36 hours following TTS application. Blood samples were collected for serum fentanyl analysis at 0, 12, and 24 hours following TTS application and at 12 hours after removal. The TTS site was examined following removal for evidence of local reaction. Efficacy of the TTS system was determined by the following: 1) rate of morphine use over the 36 hour observation period, 2) hourly rating of subjective experience of pain intensity on a 10 point analog scale, 3) global rating by observer and patient of pain control, and 4) an exit interview in which the patient was asked to evaluate her overall experience. Statistical significance of data was analyzed using PC-SAS Version 6.02.

Results - 28 patients received TTS (fentanyl)-50 and 26 received TTS (placebo). Patients in both groups were similar in age, race, ASA class and surgical procedure. 65% of TTS fentanyl patients required no supplemental analgesia from the time they left PACU (two hours postop) through the time of TTS removal (24 hours after application) compared to 4% of placebo patients. Patients treated with TTS (fentanyl)-50 required supplemental morphine administration postop at a significantly lower rate than did placebo treated patients (Table 1). For the first 36 hours postoperatively, mean morphine usage in the TTS-fentanyl group was 13.5 mg compared to 35.5 mg in the placebo group. Mean hourly pain intensity scores were significantly lower in the fentanyl treated patients compared to placebo patients (Table 2). Nurse observer ratings indicated that 88% of TTS fentanyl treated patients had excellent/very good pain control during the 24 hour treatment period versus 38% of placebo treated patients. Over 90% of patients on exit interview reported that TTS (fentanyl) caused them no problems and that they would request it again for postop analgesia following future surgical procedures. Serum fentanyl concentrations were relatively constant throughout the 24 hour period of patch application and at 12 hours following removal (Table 3).

No serious adverse reactions occurred. 46% of fentanyl treated patients and 38% of placebo patients complained of one or more mild adverse reaction postoperatively; the most commonly reported adverse effect was nausea and vomiting (39% of fentanyl patients versus 31% of placebo patients). Sedation measurements were comparable between treatment groups. Mean respiratory rates were lower in fentanyl treated patients but no patient had respiratory depression of clinical significance. Nine fentanyl treated patients and 10 placebo patients developed erythema around the patch felt to be due to irritation from the plastic edge of the patch rather than from its contents.

Discussion - For patients undergoing lower abdominal surgery transdermally delivered fentanyl at 50 ug/hr produced sustained postoperative analgesia significantly greater than placebo, with a reduced need for parenteral opioids without significant adverse effects. Transdermal fentanyl in doses of 100 ug/hr and 75 ug/hr have been reported to produce reliable base line analgesia with reduced morphine requirements for patients suffering severe or moderately severe postoperative pain.[1,2] The present study has demonstrated that transdermal fentanyl delivered in a dose of 50 ug/hr has efficacy and safety for providing pain relief following lower abdominal surgical procedures associated with moderate postoperative pain.

TABLE 1 Morphine mg/hr (0-36 hr post-op)

Fentanyl	Placebo	p Value
0.4 ± 0.5	1.2 ± 0.6	<0.001

TABLE 2 Pain Intensity Rating (0=no pain, 9=worst pain)

Hours Postop	Fentanyl	Placebo	p Value
0-2	6.0 ± 3.0	7.1 ± 1.7	0.428
2-12	4.3 ± 2.2	5.6 ± 1.9	0.075
12-24	2.2 ± 1.8	4.2 ± 1.8	0.001

TABLE 3

	Hours After Application		
	12	24	36
Serum Fentanyl Conc (ng/ml)	0.86± 0.45	1.04 ± 0.43	0.75± 0.47

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TITLE: POSTOPERATIVE PAIN RELIEF IN CHILDREN FROM THE PARASCALENE INJECTION TECHNIQUE

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Introduction. Regional anesthesia in the pediatric population is becoming increasingly commonplace. While caudal and spinal techniques are well-documented, reports of peripheral nerve blocks in this patient population remain sparse. The parascalene approach to the brachial plexus, as previously reported by Dalens[1] based upon cadaveric and clinical data, has proven to be easier and more reliable and almost devoid of complications when combined with the use of a peripheral nerve stimulator and insulated needle.

The purpose of this study was to determine the efficacy of postoperative pain relief in children, infants, and adolescents who received an intraoperative parascalene injection of local anesthetic.

Methods. This study was approved by the Human Research Review Committee of Children's Hospital of Wisconsin. After informed consent from parents, patients aged 7 months to 18 years, of ASA class I or II, and having elective upper extremity procedures were randomized into two groups. Both groups received non-narcotic, vapor-based general anesthesia after intravenous or inhalation induction by patient preference. The patients in the study group received a parascalene injection of 0.5 cc/kg of 0.25% bupivacaine with 1:200,000 epinephrine using the Dalens[1] approach, while the control group received a subcutaneous needle puncture without local anesthetic injection.

All blocks were performed by the investigator at the conclusion of surgery, with correct needle placement confirmed by twitch production using a low-output nerve stimulator attached to a sheathed, B-bevel needle. Patients in both groups were then evaluated by a research assistant, unaware of anesthetic technique, using a standardized pain and discomfort scale[2]. The patients' opioid requirements and side effects were recorded for the first 12 postoperative hours. Parametric data were analyzed by analysis of variance using Student's t-test, and non-parametric data compared with Fisher's exact test.

Results. Seven patients received a parascalene local anesthetic injection, and six patients served as controls. There were no significant differences in age, duration of operation, or duration of intraoperative anesthesia.

The percent of patients who required narcotics by 2, 4 or 6 hours postoperatively was significantly less ($p<0.02$) in the scalene group (figure 1). Because of declining narcotic requirements with time postoperatively, this effect was not statistically significant at 12 hours ($p=0.06$). While pain scores in the recovery room were not quite statistically different (figure 2, $p=0.058$), the percent of patients judged analgesic (pain score less than 3) was 100% in the scalene group vs. 17% in the control group ($p<0.005$). Time to discharge from the recovery room was not statistically less in the scalene group (50 vs. 75 minutes, $p=0.17$, figure 3). The incidence of nausea and vomiting was similar in both groups (1/7 scalene patients vs. 1/6 controls). No complications in either group were noted.

Discussion. The parascalene brachial plexus block was shown to significantly decease the perioperative opioid requirement, and to significantly increase the incidence of postoperative analgesia. Efficacy of the parascalene approach seemed universal, since none of the study patients required narcotics in the first 12 hours. Patients in the control group who were not analgesic required multiple interventions in the recovery room for narcotic administration, while patients in the scalene group could be consoled with TLC measures alone. In conclusion, we found the parascalene approach with the aid of nerve stimulation relatively easy to perform even in the small child, and an effective analgesic modality following upper extremity procedures in children.

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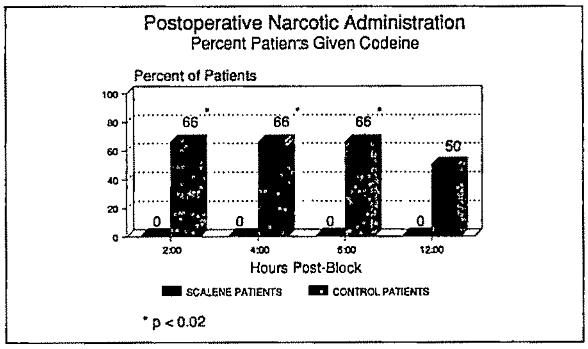

Figure 1

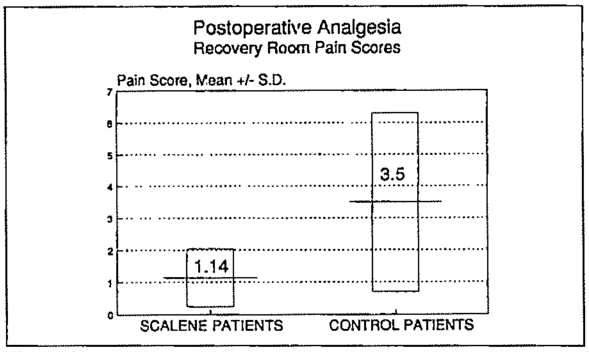

Figure 2

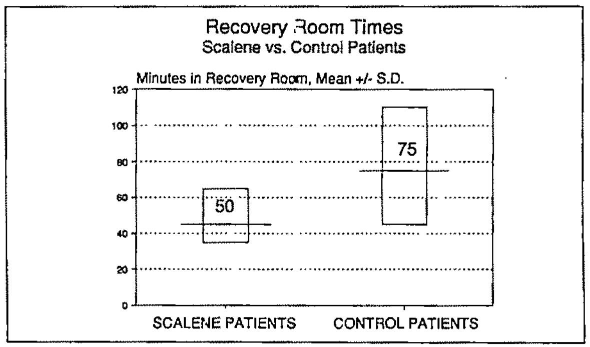

Figure 3

Single Dose Thiopental Compared to Infusion for Central Nervous System Protection During Cardiopulmonary Bypass

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INTRODUCTION:

We previously demonstrated that thiopental infused throughout cardiopulmonary bypass (CPB) reduced persistent CNS deficits after open chamber cardiac operations (1). This technique was associated with increased requirement for inotropes at weaning from CPB and prolonged emergence from anesthesia. We therefore designed a study to determine if a single lesser dose of thiopental given as a bolus before aortic declamping would provide the same brain protection as an infusion with less associated unwanted effects.

METHODS:

One hundred adult patients scheduled for open-chamber cardiac operations received neuropsychiatric examinations the day before operation. Patients in the control group received thiopental by infusion during CPB as described previously (1) thiopental dose was sufficient to produce EEG burst suppression with greater than 60 sec between bursts during the entire period of CPB. Patients in the study group received a single dose of thiopental 15 mg/kg given just before aortic declamping. Additional thiopental was given if appropriate EEG burst suppression was not achieved. Patients were otherwise managed identically. Hypothermia to 28-30°C was used to supplement myocardial protection when the aorta was cross-clamped. Use of inotropic drugs for separation from CPB and times to first response to voice and extubation were recorded. A limited neuropsychiatric examination was repeated on the first postoperative day and a full examination on the tenth postoperative day. New neuropsychiatric signs present on postoperative day one but not on day ten were considered transient; those present on both examinations were considered persistent. (Study was approved by the Institution's Internal Review Board)

RESULTS:

Patients in the bolus group received less thiopental than those in the infusion group (Table 1). Neither total nor persistent CNS deficit rates differed between groups (Table 1). Requirements for inotropic boluses and infusions did not differ between groups. Times to first response and extubation were shorter in the bolus thiopental group (Table 1). Forty three of 48 bolus patients achieved appropriate EEG burst suppression with the initial 15 mg/kg bolus. The maximum thiopental required for any patient was 26 mg/kg (1880 mgs).

DISCUSSION:

Thiopental given as a single bolus immediately prior to aortic declamping provided the same brain protection as a continuous infusion. Compared to infusion, bolus thiopental slightly reduced awakening time, but did not alter the need for inotropic support on weaning from CPB.

TABLE 1

	Infusion	Bolus
Number of Pts	52	48
Thiopental (mg/kg)	36 ± 10	16 ± 2*
Total deficits (n)	3 (6%)	2 (4%)
Persistent deficits (n)	1 (2%)	0
Inotrope bolus (n)	23 (44%)	20 (42%)
Inotrope infusion (n)	5 (10%)	6 (13%)
1st response (hrs)	8.8 ± 3.0	7.8 ± 2.8*
Extubation (hrs)	18.3 ± 5.9	16.8 ± 5.3*

* = Significant diff between groups (P 0.05)

REFERENCE:

1. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986; 64:164-170.

TITLE: **INTRAVENOUS BUTORPHANOL DECREASES THE INCIDENCE OF EPIDURAL MORPHINE INDUCED PRURITUS IN CANCER PATIENTS**

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Introduction: Concomitant infusions of opiate antagonists have been shown to decrease the incidence of side effects in patients receiving epidural narcotics.[1,2] Of the side effects, pruritus, nausea, vomiting, urinary retention and respiratory depression, the former is the most common and is often troublesome enough to warrant discontinuation of the catheter. In the present study, we infused intravenous butorphanol concomitantly in order to decrease the incidence of side effects.

Methods: Twenty-four consecutive patient charts were reviewed to evaluate the occurrence of pruritus. Informed consent for post operative epidural analgesia was obtained from all patients. All catheters were placed in the lumbar area using a loss of resistance technique and advanced 3 to 4 cm into the epidural space. Catheters were placed at the completion of the operation while the patients were under general anesthesia and the first dose of morphine (4-6 mg) was injected. Pre-printed epidural narcotic order sheets were placed in each patients chart. One milligram of butorphanol was added to each liter of intravenous fluid. The rate or infusion was left to the clinicians discretion; thus, the dose of butorphanol was variable. Subsequent epidural morphine injections were performed by a member of the Anesthesia Care Team who documented date, time and amount of injection. A daily progress note addressed quality of pain relief and presence of side effects. At our institution, Nursing Service uses the Assessment Intervention Response system for charting, which requires a note every eight hours, unless a specific incident requiring attention, or intervention, circumvenes. All catheters were removed by a member of the Anesthesia Team and a note addressing the reason for removal and state of the catheter was written.

RESULTS: Eighty-eight percent (21/24) of the patients experienced no itching with a butorphanol infusion range of 1.3 to 2.4 μg/kg/hr. Only three patients experienced episodes of itching. The procedures performed were total abdominal hysterectomy (11), thoracotomy (4), cystoprostatectomy (2), orchiectomy (2), hepatic lobectomy (1), colostomy revision (1), hip disarticulation (1), nephrectomy (1) and thigh fibrosarcoma excision (1). Pain relief was acceptable in all patients and no catheters were removed secondary to side effects. One of the three patients who developed itching had her IV discontinued. it was restarted, as was the butorphanol, secondary to a deteriorating pulmonary status and the itching subsided. The two other patients received less than 1 μ/kg/hr of butorphanol. Therefore, the incidence of itching in patients who received greater than 1 μ/kg/hr of butorphanol was zero.

DISCUSSION: In this study, a continuous intravenous infusion of butorphanol appeared to have an inhibitory effect on pruritus. Several studies in similar patient groups have shown an incidence of pruritus of 22 - 45% without a concomitant infusion.[3,4] As naloxone was shown to reverse analgesia at higher doses, a mixed agonist - antagonist with only antagonist properties at the mu receptor was used.[1] The mu receptor is responsible for mediating pruritus. That there may be functional differences between peripheral and central mu receptors was demonstrated by showing quaternary naloxone substances, which don't cross the blood brain barrier, reverse aversion/hyperalgesia, yet maintain analgesia.[5] The modulating effect butorphanol had on side effects in this study should serve to further stimulate research on opiate receptors and their agonist/antagonist substances.

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4. Gieraerts R, et al. Anesth Analg 1989;68:5101
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TITLE: LACK OF CORRELATION BETWEEN ELECTROENCEPHALOGRAPHIC AND HEMODYNAMIC CHANGES DURING GENERAL ANESTHESIA
AUTHORS: A.K. Mills, M.D. A. Ghouri, T.G. Monk, M.D., P.F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO 63110

Introduction: It has been suggested that the electroencephalogram (EEG) spectral edge frequency (SEF) can be useful in studying the depth of anesthesia(1). Although some investigators have reported that changes in EEG-SEF correlate with hemodynamic response to laryngoscopy and intubation(2), others have found no consistent relationship between hemodynamic responsiveness to surgical stimulation and changes in EEG-SEF(3). We designed a prospective study to evaluate the relationship between EEG and hemodynamic changes during general anesthesia.

Methods: 78 consenting ASA II-III adult males undergoing elective radical prostatectomy procedures were studied according to an IRB-approved protocol. Patients with known neurologic or cerebrovascular disease were excluded. Premedication consisted of midazolam 0.1 mg·kg^{-1} im. Anesthesia was induced with alfentanil 30 µg·kg^{-1}, thiopental 2.5 mg·kg^{-1} and vecuronium 0.1 mg·kg^{-1} iv, and maintained with an alfentanil infusion 0.5 µg·kg^{-1}·min^{-1}, nitrous oxide 67% in oxygen and vecuronium 0.8 µg·kg^{-1}·min^{-1}. Mean arterial pressure (MAP) and heart rate (HR) were continuously monitored. A Neurotrac EEG device with subcutaneous needle electrodes was used to record the 2-channel raw EEG signal. EEG tracings were obtained 1-2 min prior and 2-4 min after induction of anesthesia, 2-4 min after endotracheal intubation, and 1-2 min before and 2-4 min after skin incision. All EEG tracings were evaluated by a blinded observer experienced at reading Neurotrac EEG recordings. The SEF was determined from the compressed spectral array. Data were analyzed using ANOVA with repeat measures, and correlation coefficients were calculated for the curves relating hemodynamic and EEG changes.

Results: In this homogenous male study population (age 63±3 yr, weight 85±6 yr) undergoing similar operations, marked variability was noted in the relationship between hemodynamic and EEG changes. Although SEF decreased following induction of anesthesia and increased following skin incision (Table 1), there were no obvious correlations between EEG activity and MAP or HR during the operation. Figures 1A and 1B display the lack of correlation between EEG-SEF and changes in MAP following induction of anesthesia and endotracheal intubation. Figure 1C summarizes the relationship between changes in EEG-SEF and changes in MAP following skin incision. Similarly, there was no correlation between changes in HR and SEF at induction, intubation, and skin incision.

Discussion: In contrast to Rampil and Matteo, we were unable to correlate changes in EEG-SEF and MAP during general anesthesia. Irrespective of whether the MAP was decreasing (induction) or increasing (laryngoscopy and skin incision), the magnitude of the hemodynamic response failed to correlate with the changes in EEG-SEF. Possible explanations for the differences in our results include different surgical populations (e.g. ASA I vs ASA II-III, young vs older, no chronic medications vs beta and calcium channel blockers), anesthetic techniques (thiopental vs midazolam-alfentanil-thiopental), and algorithms for analyzing the EEG signal. Although the Neurotrac EEG monitor may be a clinically useful indicator of cerebral blood flow, it would appear to be of limited (if any) value as a monitor of "depth of anesthesia."

References:
(1) Hudson R, Stanski D et al. Anesthesiology 1983;59:301-8.
(2) Rampil IJ, Matteo RS. Anesthesiology 1989;67:139-42.
(3) White PF, Boyle WA. Anesth Analg 1989;68:177-81.

Table 1: Changes in hemodynamic and EEG variables during general anesthesia (Mean values ± S.D.)

Event	ΔMAP (mmHg)	ΔHR (bpm)	ΔSEF (Hz)
Induction	-16±12*	-5±8*	-1.7±5.1*
Intubation	13±16*	0±9	0.2±3.9
Skin incision	16+10*	1+8	1.0+4.5

* Significant difference between pre- and post- values, p<0.05

FIGURE 1A: INDUCTION

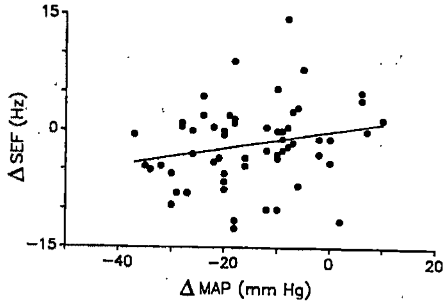


FIGURE 1B: INTUBATION

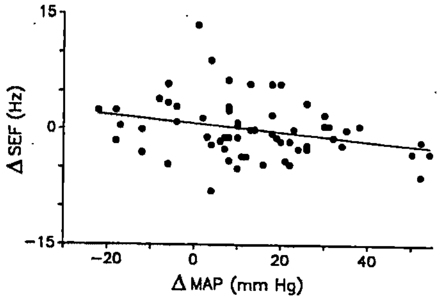
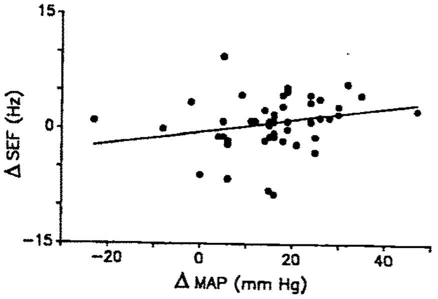


FIGURE 1C: SKIN INCISION



TITLE: COMPARATIVE EFFECTS OF CENTRAL VS PERIPHERAL-ACTING DRUGS ON THE EEG DURING GENERAL ANESTHESIA

AUTHORS: A.K. Mills, M.D., T.G. Monk, M.D., P.F. White, Ph.D., M.D.
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Introduction: The electroencephalogram (EEG) has been used to assess the central nervous system effects of anesthetic and analgesic drugs (1,2). In addition, some investigators have suggested that the EEG can be useful in determining the "depth of anesthesia." We designed a study to evaluate the effects of isoflurane, alfentanil and trimethaphan on the EEG spectral edge frequency (SEF) and hemodynamic responses to surgical stimulation during general anesthesia.

Methods: Seventy-seven consenting patients undergoing major intra-abdominal surgery were studied according to an IRB-approved protocol. All patients were premedicated with midazolam 0.1 $mg \cdot kg^{-1}$ im. Anesthesia was induced with alfentanil 30 $\mu g \cdot kg^{-1}$, thiopental 2.5 $mg \cdot kg^{-1}$ and vecuronium 0.1 $mg \cdot kg^{-1}$ iv. Maintenance of anesthesia consisted of alfentanil 0.5 $\mu g \cdot kg^{-1} min^{-1}$, nitrous oxide 67% in oxygen, and vecuronium 0.8 $\mu g \cdot kg^{-1} min^{-1}$. Mean arterial pressure (MAP) and heart rate (HR) were continuously monitored. A Neurotrac EEG device with subcutaneous needle electrodes was used to record the two-channel raw EEG signal. All patients manifested a >15% increase in MAP upon entering the abdominal cavity (pre-Rx). After obtaining a baseline raw EEG tracing and a compressed spectral array (CSA) with spectral edge frequency (SEF), patients were administered either; (1) alfentanil 20-60 $\mu g \cdot kg^{-1}$, (2) trimethaphan 0.05-0.15 $mg \cdot kg^{-1}$, or (3) isoflurane 0.5-1.0% to return the MAP to within 10% of the pre-incision value. The EEG analysis was repeated after normalization of the MAP (post-Rx). Comparisons of pre-Rx and post-Rx hemodynamic and EEG variables were performed using ANOVA, with $p<0.05$ considered statistically significant.

Results: The three drug treatment groups were comparable with respect to demographic data and baseline hemodynamic and EEG values (Table 1). The three study drugs produced comparable effects on MAP, HR, and EEG-SEF (Table 2). Irrespective of whether the MAP (HR) was increasing in response to surgical stimulation (Fig. 1) or decreasing in response to drug treatment (Figs. 2A-D), there was no correlation between MAP (HR) and EEG-SEF.

Discussion: These data indicate that while a decrease in EEG-SEF activity occurs following treatment of acute hypertensive responses to surgical stimulation, the EEG response produced by the peripherally-acting vasodilator (trimethaphan) did not differ from that which was achieved with the centrally-acting analgesic (alfentanil) or the inhalational anesthetic (isoflurane). In addition, the EEG response failed to correlate with the increase in MAP following skin incision. Thus, it would appear that the EEG response may reflect changes in cerebral blood flow rather than changes in "depth of anesthesia."

Table I: Demographic, pre-treatment hemodynamic and EEG values and changes (Δ) with drug treatment (Mean ± S.D.)

	Alfentanil	Trimethaphan	Isoflurane
Age (yr)	64±9	64±10	66±8
Weight (kg)	85±12	82±12	80±11
Pre-Rx			
MAP (mm Hg)	117±14	123±13	124±16
HR (bpm)	58±12	62±14	62±11
SEF (Hz)	15.7±3.9	18.1±5.6	17.7±5.2
ΔMAP (mm Hg)	-21±10	-24±10	-19±14
ΔHR (bpm)	-5±8	0±10	-3±9
ΔSEF (Hz)	-3.4±4.0	-3.6±6.0	-3.8±4.5

References:
1. Hudson RJ, Stanski DR, Saidman LJ, Meathe E. Anesthesiology 1983;59:301-8.
2. Smith N, et al. Anesth Analg 1984;63:386-93.

FIGURE 1: INCREASE IN BLOOD PRESSURE (OVERALL)

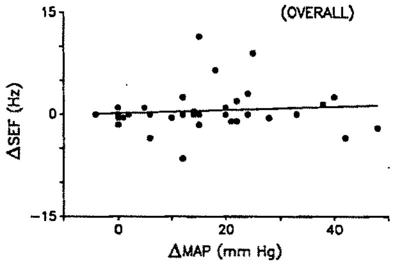


FIGURE 2A: DECREASE IN BLOOD PRESSURE (OVERALL)

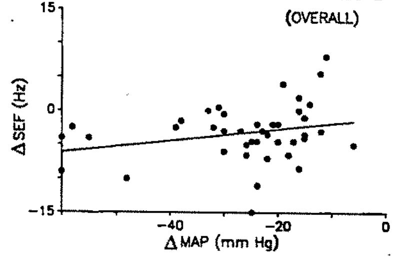


FIGURE 2B: DECREASE – ALFENTANIL

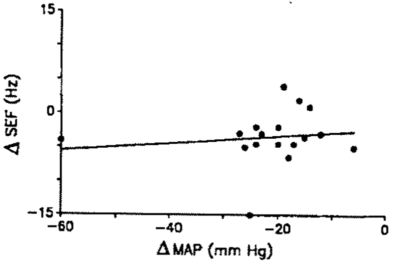


FIGURE 2C: DECREASE – TRIMETHAPHAN

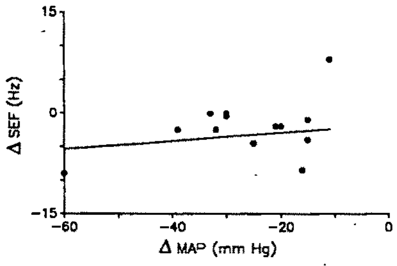
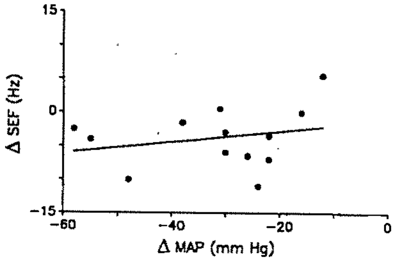


FIGURE 2D: DECREASE – ISOFLURANE



TITLE: NERVE DISTRIBUTION PATTERNS WITHIN PREPUCIAL TISSUE: CLINICAL APPLICATIONS IN PENILE NERVE BLOCKS

AUTHORS: R.MOLDWIN, M.D. AND E. VALDERRAMA, M.D.
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INTRODUCTION: Typically, anesthesia has not been employed during neonatal circumcisions due to assumptions of decreased pain sensation.[1] Recently, a plethora of clinical information has been forwarded suggesting a severe degree of pain experienced by infants during such procedures.[2]

To further examine neonatal penile sensory development on an end organ level, we examined prepucial tissue from patients of varying ages undergoing cosmetic circumcision. Specimens were analyzed histologically for patterns of nerve distribution and density. Our aim was to examine changes in these parameters with aging. Patterns of peripheral nerve distribution might have clinical relevance in terms of the most effective nerve blockade administered during penile surgical procedures.

METHODS AND MATERIALS: Patient selection:

Prepucial tissue was obtained from 35 patients undergoing cosmetic circumcision. Patients ranged in age from newborn to 52 years of age. The age distribution was: Newborn to 1 year(group 1)-18 patients; 1 year to 5 years(group 2)-11 patients; and, 5 years to adulthood(group 3)-6 patients. **Histochemical analysis**: Cross sections of paraffin embedded tissue were then analyzed using rabbit anti-human neuron specific enolase (NSE) immunohistochemistry (Dakopatts Labs), and Bodian's silver and hematoxalin-eosin stains.

RESULTS: The most striking histologic feature of all examined prepucial specimens was the reliable distribution of nerve bundles within the dermis and subcutaneous tissue. A disproportionately high number of bundles (mean=16.2 bundles/mm2; standard deviation (s.d.)2.3) was observed in ventral tissue as opposed to lateral (mean=9.3 bundles/mm2; s.d. 2.1) and dorsal tissue (mean=7.4 bundles/mm2; s.d. 1.5). Nerve bundles examined in groups 1 and 2 were predictably smaller than in group 3. Nerve bundles within the subcutaneous tissue of adults were as large as 0.2 mm in diameter as opposed to groups 1 and 2 whose largest bundles were 0.05mm in diameter. This discrepancy appeared to arise from the large degree of hypertrophy and myelination acquired with age.

Large numbers of unmyelinated nerve endings were noted within dermal papillae. These fibers appeared to project to the epidermal basal lamina and in many instances to the stratum basale.

DISCUSSION: These data suggest that a complex sensory neuronal plexus exists in the newborn, and excludes the possibility of decreased prepucial sensation on the basis of a poorly developed end nerve supply.

Furthermore, we have shown a statistically higher nerve density within the ventral prepucial skin in all age groups examined. These nerve bundles appear to arise from ventral projections of the dorsal nerve of the penis or the direct projections of the perineal nerve. The ventral course of the perineal nerve may explain the frequent difficulty in anesthetizing ventral penile skin with a dorsal nerve block.

Most current literature advocates the use of a dorsal penile nerve block during neonatal circumcision.[3] Our data, however, suggest that a dorsal nerve block may be insufficient to achieve complete anesthesia for two reasons: 1. If an adequately "high" block (as the nerve exits the inferior margin of the suspensory ligament) is not administered, a large number of ventrally deviating branches will be spared; and, 2. The sensory contribution of the perineal nerve will remain intact.

To avoid these difficulties and to provide the maximum pain relief in the neonate, we recommend a simultaneous circumferential nerve block. This additional block adds little time to the overall procedure and can usually be performed through the initial puncture site of the dorsal penile nerve block.

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3.Lau,JT. Penile block for pain relief after circumcision in children. Am.J.Surg. 1984; 147:797-9.

Title: HEMODYNAMIC, STRESS HORMONE AND LEC RESPONSES DURING GENERAL ANESTHESIA

Authors: T.G. Monk, M.D., A.K. Mills, M.D., P.F. White, Ph.D., M.D.
Affiliation: Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO 63110

Introduction: Assessing the adequacy of anesthesia when using a nitrous oxide - narcotic - relaxant technique remains a difficult problem. Clinical determination of "depth of anesthesia" usually involves evaluating hemodynamic, somatic, and autonomic responses to surgical stimuli. Since these responses are altered by a wide variety of physiologic and pharmacologic factors, a reliable non-invasive monitor of anesthetic depth would be extremely valuable. It has been suggested that measurements of lower esophageal contractility (LEC) could be useful in judging depth of anesthesia (1). We designed a study to examine the relationship between changes in hemodynamic variables, stress hormone levels and LEC activity in response to surgical stimulation and to treatment of "light" anesthesia with an inhalational agent.

Methods: Sixty-four consenting males (ASA II-III) undergoing radical prostatectomy operations were studied according to an IRB-approved protocol. All patients were premedicated with midazolam 0.1 mg.kg^{-1} im. Anesthesia was induced with alfentanil 30 ug.kg^{-1}, thiopental 2.5 mg.kg^{-1} and vecuronium 0.1 mg.kg^{-1}, iv. Maintenance of anesthesia consisted of an alfentanil infusion 0.5 ug.kg^{-1}.min^{-1}, nitrous oxide 67% in oxygen, and vecuronium 0.8 ug.kg^{-1}.min^{-1}. Mean arterial pressure (MAP) and heart rate (HR) were continuously monitored. A Lectron 302 monitor was used to continuously measure the LECI (an index which reflects both spontaneous and provoked LEC activity)(2). Blood samples for determination of catecholamines, B-endorphin, and vasopressin levels were obtained 1-2 min. before skin incision (Pre-Inc) from a central venous catheter. All patients manifested a >15% increase in MAP upon entry into the abdominal cavity. Mixed venous blood samples for measurement of stress hormone levels were obtained 1-2 min. after entering the abdominal cavity (Post-Inc). Comparisons of Pre-Inc and Post-Inc MAP and HR values, plasma hormone concentrations, and LECI were measured. In a subgroup of patients (n=22), isoflurane (0.5-1.0%) was administered to treat the Post-Inc hypertensive response. All measurements were repeated after normalization of the MAP (Post-Rx). Data were analyzed using ANOVA with repeated measures, $p<0.05$ was considered significant.

Results: In this homogenous male surgical population (age 65±8 yr, height 176±7 cm, weight 82±12 kg), we found no correlation between hemodynamic, stress hormone and LECI changes in response to surgical stimulation or to treatment of an acute hypertensive response with isoflurane. Although the average MAP and stress hormone levels increased significantly from the Pre-Inc values in response to the surgical stimulation (Table 1), the LEC index did not significantly change. Furthermore, there was no correlation between the increase in MAP and LECI (Fig. 1) or the decrease in MAP and LECI (Fig. 2). Similarly, changes in stress hormone levels, did not correlate with LECI (Fig. 3). Although the stress hormone levels returned to their Pre-Inc values after treatment, the LECI value was unchanged.

Discussion: Measurements of LEC were reported to correlate with general anesthetic depth (1). Although the mean LECI values in our study remained within the range (30-120) which was alleged to correlate with surgical anesthesia (2), our patients exhibited clinical, hemodynamic, and stress hormone changes consistent with "light" anesthesia following skin incision. This response was effectively treated by administering isoflurane; however, the LECI was non-significantly decreased. If one assumes that significant increases in MAP (and/or HR) are indicative of inadequate anesthesia, LEC does not appear to correlate with "depth of anesthesia" in this surgical model.

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(1) Evans JM, Davies WL, Wise CC. Lancet 1984;ii:1151-4.
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Table 1: Changes in MAF, HR, LECI and stress hormone levels following surgical stimulation and treatment (mean ± S.D.)

	Pre-Inc	Post-Inc	Post-Rx
MAP (mmHg)	90±14	122±14*	95±11
HR (bpm)	55±10	62±12*	60±13
LECI (index)	86±114	97±99	61±67
Epinephrine (pg·ml^{-1})	30±18	98±112*	45±33
Norepinephrine (pg·ml^{-1})	335±183	534±299*	505±328
Total catecholamines (pg·ml^{-1})	378±193	656±356*	580±344
B-endorphin (pg·ml^{-1})	28±12	46±43*	31±11
Vasopressin (pg·ml^{-1})	12±40	39±49**	7±11

*$p<0.05$; **$p=0.06$ vs. Pre-Inc value

FIGURE 1: ΔLECI vs ΔMAP (OVERALL)

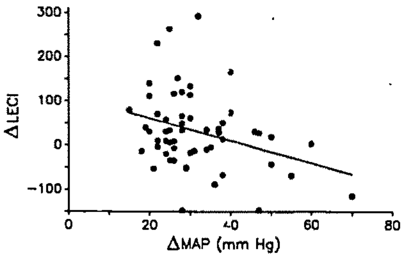


FIGURE 2: ΔLECI vs ΔMAP (ISOFLURANE)

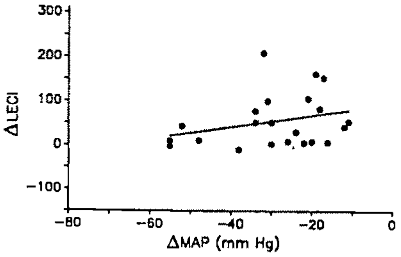
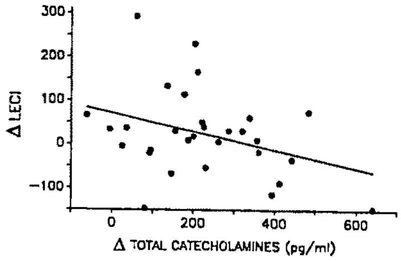


FIGURE 3: ΔLECI vs ΔTOTAL CATECHOLAMINES



Title: USE OF PCA IN GERIATRIC PATIENTS - EFFECT OF AGING ON THE POSTOPERATIVE ANALGESIC REQUIREMENT

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Introduction. It is widely accepted that elderly patients have a decreased requirement for analgesic drugs (1). More recent studies have suggested that pharmacodynamic factors are involved in the enhanced sensitivity of the elderly to the central nervous system (CNS) effects of opioid analgesics (2). We examined the effect of aging on the postoperative analgesic requirement when patients were allowed to self-administer opioid medication using a patient-controlled analgesic (PCA) device. In addition, we examined the effect of aging on the relationship between drug usage, pain relief, and side effect profile.

Methods. After obtaining IRB approval, 151 consenting patients (aged 40-80 yr), who had undergone either a radical prostatectomy (Group I, n=71) or a hysterectomy (Group II, n=80) procedure with a standardized anesthetic technique were allowed to self-administer morphine using a PCA delivery system. In the recovery room, patients were connected to an Abbott Lifecare™ PCA infusor programmed to deliver morphine 2 mg iv bolus injections "on demand". Morphine usage was determined at 8h intervals during the first three postoperative days. Pain scores were determined using 100mm analog scales. Side effects and overall satisfaction with the PCA therapy was assessed using a follow-up questionnaire. Data were analyzed using ANOVA and Chi square tests, with $p<0.05$ considered significant.

Results: Demographic data regarding patient height, weight, duration of anesthesia, and length of hospital stay were similar for all age ranges within each treatment group (Table 1). In the elderly (>70 yr) patients, the average daily morphine requirement was decreased 24-61% and 15-24% in Groups I and II, respectively, compared to the younger (<50 yr) patients (Table 2). Although the side effect profiles were similar among the various age groups, the elderly patients experienced less pruritis (Table 3). Overall adequacy of pain relief and patient preference for future analgesic therapy indicated that PCA was well-accepted by most elderly men and women. However, compared to younger patients undergoing similar operations, elderly patients were less satisfied with their pain relief and PCA therapy.

Discussion: When allowed to self-titrate opioid analgesics using a PCA delivery system, elderly patients tended to administer less medication and achieved less satisfactory pain relief. Given these data, it would appear that the decreased analgesic requirement in the elderly (vs younger) patients may be related in part to differing expectations regarding postoperative pain relief and/or a lack of understanding of PCA therapy. In addition, enhanced sensitivity to morphine's CNS effects may account for the high incidence of excessive sedation in the elderly Group II patients. Further studies are needed to determine the factors which influence the PCA dosage requirement.

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(1) Bellville JW, Forrest WH, Miller E, et al: Influence of age on pain relief from analgesics. JAMA 1971;217: 1835-41.
(2) Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age. J Pharmacol Ther 1987;240: 159-66.

Table 1: Demographic data for patients undergoing either radical prostatectomy (Group I) or hysterectomy (Group II)

	Group I			Group II		
Age range (yrs)	No. (n)	Weight (Kg)	Anesthesia Time (min)	No. (n)	Weight (Kg)	Anesthesia Time (min)
40-49	5	85±18	242±45	38	76±22	185±82
50-59	11	82±14	275±50	13	70±11	169±41
60-69	33	84±11	293±50	16	72±16	209±74
70-79	22	81±11	294±89	11	68±13	206±50

Table 2: Daily morphine usage (mg per 24h) for Groups I and II

Age range	Group I (Prostatectomy)			Group II (Hysterectomy)		
(yrs.)	Day #1	Day #2	Day #3	Day #1	Day #2	Day #3
40-49	41±17	34±26	23±26	59±25	40±22	44±22
50-59	54±16	32±16	17±11	52±19	41±15	40±14
60-69	44±17	24±19	21±17	43±12	37±13	32±14
70-79	31±14	22±19	9± 6	45±21	34±22	35±20

Table 3: Pain assessment, side effects and patient satisfaction with PCA therapy (percent of patients in each age group)

Age Range (yrs)	Severe Pain	Excessive Sedation	Nausea/ Vomiting	Pruritis	Ease of Use	Adequate Therapy	Prefer PCA
Group I (prostatectomy)							
40-49	0	0	0	40	100	95	100
50-59	9	9	10	18	100	100	100
60-69	9	3	9	15	100	100	94
70-79	29	0	15	0	95	100	75
Group II (hysterectomy)							
40-49	7	0	0	14	98	98	91
50-59	7	7	10	33	100	100	93
60-69	7	19	14	40	100	93	93
70-79	25	33	17	18	91	92	83

Title MATERNAL AND NEONATAL PLASMA CATECHOLAMINE LEVELS FOLLOWING EPIDURAL EPINEPHRINE ADMINISTRATION

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Introduction: Epinephrine is often added to local anesthetics to produce lumbar epidural anesthesia (LEA) in parturients. Epinephrine is absorbed into the maternal systemic circulation and produces β-effects. Currently, no data exist on the maternal and fetal plasma levels of epinephrine (Epi) and norepinephrine (Norepi) in obstetrical patients receiving Epi for LEA.
Methods: The study was approved by the local review board and patients gave informed consent. A total of 16 healthy patients were randomly divided into two groups. One group received 0.5% bupivacaine with Epi (1:200,000) for LEA for elective cesarean section and the other group received only bupivacaine. In all patients, 1500 ml of Ringers lactate was given for intravenous hydration. An L2-L3 or an L3-L4 catheter was placed for LEA and a T4 sensory level was achieved by injecting the anesthetic in 5 ml increments. Left uterine displacement was maintained. Maternal venous blood samples were drawn from an indwelling cannula for measurement of Epi and Norepi at the following time intervals: baseline, T6 sensory level, delivery, 10, 20, and 30 min after delivery. Samples were also collected from the umbilical vein and artery (UV and UA). Maternal arterial and UV and UA blood pH, PO_2, and PCO_2 were measured. A high performance liquid chromatograph (Waters 712 WISP HPLC) with an electrochemical detector was used for measuring catecholamines. Results were expressed as mean ± 1SE and analyzed for significance using t-test.
Results: The groups did not differ significantly in age, height, or weight. No significant differences were noted between maternal or neonatal blood pH, PCO_2 and PO_2 between the two groups (Table 1). The neonatal Apgar scores were similar in both groups. Baseline maternal Epi and Norepi did not significantly differ among the groups. At all the other times, maternal plasma Epi was significantly greater in the Epi group than in the non-Epi group (Fig). No differences were noted in the maternal Norepi levels. Neonatal catecholamine levels showed a wide scatter. Neonatal UA Epi and Norepi levels were significantly higher in the Epi group than in the non-Epi group (Table 2) with no significant difference in UV Epi and Norepi levels. Three of the UV samples in the plain group did not contain measurable Epi levels while all UV samples in the Epi group did contain Epi.
Discussion: Catecholamine levels in our study are consistent with previously reported levels (1). Our data show that epinephrine administered into the maternal epidural space is rapidly absorbed into the maternal systemic circulation. Elevated levels of epinephrine persist in the maternal circulation for at least 30 min. Neonatal UA EPI levels were also high in those receiving epinephrine. Since neonatal blood pH did not significantly differ among the groups, the elevated epi levels appear to be due to placental passage and not due to fetal asphyxia. Caution must be exercised in using epinephrine for epidural anesthesia in patients with cardiac disease or preeclampsia.

Table 1: Maternal and neonatal blood pH and gas tensions.

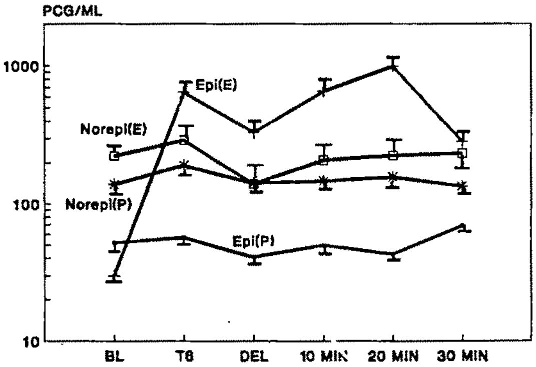
Plain Group	Maternal	Umb. vein	Umb. art
pH	7.43(0.01)	7.38(0.01)	7.31(0.01)
PO2	318 (10)	28(1)	18(2)
PCO2	34(5)	41(1)	48(3)
BE	-4.0(2)	-2.0 (1)	-1.0 (1)
Epi Group:			
pH	7.45(0.02)	7.36(0.01)	7.32(0.01)
PO2	324(11)	28(1)	18(1)
PCO2	33(5)	39(1)	48(3)
BE	-5.0(2)	-2 (1)	-1.4(1)

Legend: No significant differences were noted in any of the measurements between the groups.

Table 2: UA and UV catecholamine levels (pcg/ml).

	Plain		Epi	
	UA	UV	UA	UV
Epi	150(27)*	15(3)	910(183)	483(165)
Norepi	708(67)*	175(15)	1171 (73)	240(20)

Legend: * different from the Epinephrine group. Three UV samples in the plain group had no measurable Epi.



Legend: At all sampling intervals maternal plasma Epi levels (top-most curve) in the Epi group were higher than in the Plain group. No differences were seen in the Norepi levels. P -Plain group; E -Epinephrine group.

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Title: **Random double blind comparison of Ranitidine, Nizatidine and Placebo in reducing gastric acidity**

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Introduction: During the induction of general anæsthesia, patients are at risk of acid aspiration. Premedication with H_2 antagonists can reduce this risk. Studies comparing cimetidine and ranitidine, favour ranitidine for paucity of side effects and drug interactions, as well as its longer duration of action. The purpose of this study is to compare the efficacy of rantidine with nizatidine– a new H_2 antagonist, with a similarly favourable profile, for prophylaxis of acid aspiration.

Methods: After approval from the institutional ethics review board, informed written consent was obtained from 30 heathy, ASA 1, patients, scheduled for elective surgery. This was a double-blind study in which the patients were randomly assigned to receive either; rantidine 300 mg, nizatidine 300 mg or placebo. The pill was given by mouth with a sip of water 2 hours prior to surgery. The randomization and blinding was performed by the hospital pharmacy. No other premedication was given. Patients were fasting for a minimum of 8 hours prior to the induction of anæsthesia. The actual duration of fasting was recorded. Anæsthesia was induced with pentothal, intubation was facilitated using succinlycholine. After the patient's condition was stabilized, an 18 gauge orogastric tube was inserted and the gastric contents were aspirated. Gastric volume was measured using a calibrated syringe. Gastric pH was measured using a Corning pH meter. Samples were analyzed as soon as possible after collection. Statistical assessment of the data was performed using ANOVA and χ square analysis for parametric and nonparametric data respectively. A p value of <0.05 was considered statistically significant.

Results: In total we studied 30 subjects, 10 per group. Patients in each group were similar with respect to sex, height, weight and time fasting (Table 1). Rantidine and nizatidine were similarly effective in reducing gastric volume and increasing gastric pH (Table 2). In 3 subjects from the nizatidine group no gastric sample could be obtained, despite confirmation by insufflation of air with simultaneous auscultation. Using standard criteria that gastric volume of >25 ml and pH of <2.5 represents a patient at risk of acid aspiration, not a single patient remained at risk after pretreatment with either ranitidine or nizatidine. In contrast, 5 of the 10 patients in the placebo group (50%) remained at risk of acid aspiration.

Discussion: We conclude that ranitidine and nizatidine are similarly very effective in reducing gastric pH and volume. The mechanism of action of H_2 antagonist is to reduce gastric acid production and as a natural consequence gastric volume is reduced. Since H_2 antagonists have no direct effect on gastric emptying it is not surprising that one patient in both the ranitidine and nizatidine groups had volumes greater than 25 mls. Although pretreatment with an H_2 antagonist was effective in all patients that we studied it is unsafe to assume that H_2 antagonists will ***always*** be successful in abolishing the risk of acid aspiration.

Table 1

	Age (yr)	Weight (kg)	Height (cm)	Time fasting (min)
Ranitidine	29±9	76±17	172±11	814±138
Nizatidine	30±9	70±9	171±12	928±128
Placebo	25±4	84±22	172±12	831±115

Table 2

	Volume (ml)	pH	Volume >25 ml # Pts	pH<2.5 # Pts	At Risk # Pts
Ranitidine	7±8*	7.1±0.7*	1*	0*	0*
Nizatidine	8±9*	7.3±0.6*	1*	0*	0*
Placebo	30±18	3.0±2.6	7	7	5

* different from placebo p<0.05

TITLE: MORPHINE SULFATE AND NALBUPHINE HYDROCHLORIDE: DIFFERING EFFECTS ON HYPERCAPNIC AND HYPOXIC RESPIRATORY DRIVES IN PREMEDICANT COMBINATIONS

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Introduction. The prospect of surgery and the placement of invasive monitors is anxiogenic and painful for the preoperative patient. Therefore, premedication is important and frequently includes drugs with complimentary actions such as sedative-hypnotics and opiates. While this combination of premedicants is usually effective, it may lead to respiratory depression resulting in hypoxia and/or hypercarbia. The purpose of our study was to compare the respiratory, sedative and anxiolytic effects of two different premedications that included morphine sulfate (MS) or the antagonist/agonist nalbuphine hydrochloride (NAL).

Methods. After obtaining Institutional Review Board approval, we studied 13 healthy, consenting volunteers in a randomized, double-blind study. Subjects were assigned to undergo either hypercapnic (N=7) or hypoxic (N=6) respiratory drive studies. Each subject received two different intramuscular (IM) premedications (scopolamine, 0.003 mg/kg and lorazepam, 0.03mg/kg with MS, 0.1 mg/kg or NAL, 0.1 mg/kg) on two separate days. Subjects were continuously monitored with an ecg, blood pressure cuff and finger pulse oximeter.

The hypercapnic ventilatory drive was measured using the Read rebreathing method (1). The slope of the carbon dioxide (CO_2) response curve was determined by dividing the change in minute ventilation (V_E) by the change in end-tidal CO_2. Normocapnic hypoxic ventilatory response was assessed using the method of Rebuck et al (2). Subjects breathed from a closed circuit containing a gas mixture of 24% oxygen, $7\%CO_2$ and balance nitrogen. Oxygen (O_2) in the circuit fell as O_2 was consumed and normocarbia (±1 mmHg) was maintained using a CO_2 absorber. Hypoxic drive was quantified by dividing the change in V_E by the change in percent arterial O_2 saturation (%sat) as measured by peripheral pulse oximetry. Each hypoxic study was terminated when the arterial saturation reached 75%.

Subjects fasted overnight and all studies were performed in the morning in a quiet, dimly lit room. After familiarization with the study design, subjects underwent control evaluations of respiratory drive, alertness/sedation and anxiety. Alertness was assessed by a trained observer using a graded score (1=unresponsive to 5=fully alert). Subjects self-assessed sedation using a linear analog scale (0=awake/alert to 100=unresponsive/asleep) and anxiety was graded by an observer (1=negligible to 4=marked). Subjects then received IM premedications and were asked to describe any subjective effects. After one hour, respiratory drive, state of consciousness and anxiety assessments were evaluated. Forty-eight hours later, the subjects underwent the same evaluations receiving the other study premedication. Data were analyzed using one and two way anova. P values < 0.05 were considered statistically significant.

Results. The two groups were comparable with respect to subjects' age, weight, gender and forced vital capacity. All control hypercapnic and hypoxic response curves were within normal limits. Both premedications resulted in a similar degree of sedation and anxiolysis (table). However, subjects who compared their degree of "grogginess" from one study day to the other, all reported more profound sedation following NAL premedication. Hypoxic respiratory drive was depressed by 30% and 42% from control values in the MS and NAL premedication groups, respectively. In contrast, the ventilatory response to hypercapnia was depressed in the MS group (-30%), while the NAL group (-7%) had little change in response to increased CO_2 (figure). There were no complaints of nausea, vomiting, dysphoria, or agitation. Injection of lorazepam resulted in more spontaneous complaints of pain.

Discussion: This study demonstrates that in healthy volunteers premedications including MS and NAL have differing effects on hypercapnic and hypoxic respiratory drives. Gal et al reported that intravenous MS and NAL, in doses comparable to those of our study, did not depress CO_2 response curves (3). In contrast, we studied a combination of premedicants and found that MS but not NAL combinations resulted in depressed CO_2 ventilatory drive. However, the antagonist/agonist NAL resulted in hypoxic drive depression similar to MS. Further clinical studies are necessary to assess the effects of combination premedicants on respiratory drives. Whether NAL premedicants are advantageous in the patient with compromised CO_2 drive should be studied in an appropriate clinical model.

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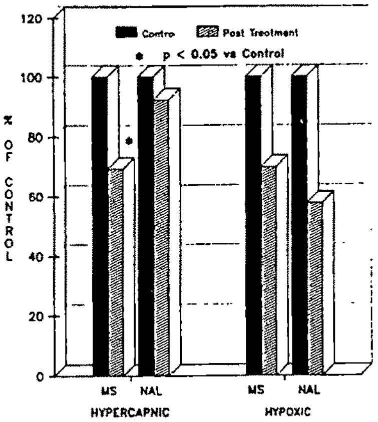
Table. Pre and post-treatment scores

	Control		Post-treatment	
	MS	NAL	MS	NAL
Anxiety Score	1.6	1.5	1.5*	1.2*
Sedation Score	1.0	1.0	2.5*	2.7*
Sedation Analog	5	7	41*	38*

* $p < 0.05$ post-treatment vs control values
NS difference between MS and NAL groups

Figure. Hypercapnic and hypoxic drives: percent changes from control to post-treatment values



TITLE: USE OF PROPOFOL DURING CARDIAC ANESTHESIA - MAINTENANCE INFUSION RATES AND THERAPEUTIC BLOOD LEVELS

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Introduction: Propofol is rapid and short-acting intravenous anesthetic which has been used to control hypertensive responses during cardiopulmonary bypass (CPB)(1). Compared to other commonly used anesthetics and analgesics (e.g. enflurane, thiopental, fentanyl), use of propofol during cardiac surgery is associated with a rapid recovery and low incidence of postoperative side effects(2,3). We evaluated the relationship between the maintenance infusion rate for propofol and the resultant blood propofol concentration before, during, and after CPB. In addition, the effect of the site of blood sampling on the measured propofol concentration was evaluated during cardiac surgery.

Methods: Twenty consenting adult male patients scheduled for elective coronary artery bypass surgery were studied according to an IRB-approved protocol. All patients were premedicated with morphine sulfate, 7.5-15 mg im, scopolamine 0.2-0.4 mg im, and diazepam 5-15 mg po one hour prior to surgery. Perioperative monitors included EKG, arterial and thermodilution pulmonary artery (PA) catheters, and EEG monitoring. Nitroglycerin, 50 $\mu g \cdot min^{-1}$ iv, was administered throughout the perioperative period. Anesthesia was induced with fentanyl, 25 $\mu g \cdot kg^{-1}$ and metocurine 0.08 $mg \cdot kg^{-1}$ /pancuronium 0.08 $mg \cdot kg^{-1}$ iv. When the MAP exceeded the post-induction (baseline) value by more than 15%, patients were administered a propofol 10-20 mg iv bolus and a maintenance propofol infusion, 5 mg/min, was started and adjusted to maintain MAP within 10% of the baseline value before CPB. During hypothermic CPB, the propofol infusion rate was adjusted (2.5-25 $mg \cdot min^{-1}$) to maintain EEG "burst suppression" and a MAP of 40-60 mmHg at a constant flow of 2.1-2.3 $L \cdot min^{-1} \cdot m^{-2}$. Before initiating CPB, the propofol infusion was administered into a peripheral vein, while it was infused directly into the bypass apparatus during CPB. The propofol infusion was discontinued at the end of CPB. Blood samples were obtained from the proximal port of the PA catheter immediately prior to increasing an inadequate or decreasing an adequate maintenance infusion rate. Samples were subsequently analyzed for propofol using an established HPLC fluorescence technique. In a subgroup of patients (n=5), simultaneous mixed venous and arterial blood samples were obtained in order to determine a-v differences in the propofol concentration. The mean effective propofol concentrations were determined before, during and after CPB by averaging the highest "inadequate" and the lowest "adequate" venous propofol concentrations during each of the specified time periods. All patients were administered an additional dose of fentanyl, 10 $\mu g \cdot kg^{-1}$, after weaning from CPB. Values are presented as means ± S.D. Data were analyzed using Student's t-test and ANOVA with regression analysis, $p<0.05$.

Results: In this male cardiac surgery population (age 63 ± 8 yrs, weight 84 ± kg and height 177 ± 7 cm), an average propofol infusion rate of 7 ± 4 $mg \cdot min^{-1}$ was required for 64 ± 21 min prior to CPB, with a mean effective blood propofol concentration of 2.9 ± 1.2 $\mu g \cdot ml^{-1}$. During CPB, the average propofol infusion rate was 10 ± 6 $mg \cdot min^{-1}$ for 54 ± 15 min and the resultant effective propofol level was 2.7 ± 1.2 $\mu g \cdot ml^{-1}$. The average propofol concentrations after CPB and at the end of surgery were 0.9 ± 0.6 and 0.5 ± 0.4 $\mu g \cdot ml^{-1}$, respectively. When simultaneous arterial and mixed venous blood samples were obtained prior to CPB, venous levels were significantly higher than arterial (2.0 ± 0.8 vs 1.2 ± 0.7 $\mu g \cdot ml^{-1}$, respectively). However, during CPB the average venous and arterial propofol concentration values were 2.5 ± 0.9 and 5.7 ± 1.1 $\mu g \cdot ml^{-1}$, respectively ($p<0.05$). After discontinuing the propofol infusion, the average venous levels again exceeded the arterial levels, 0.9 ± 0.5 vs 0.3 ± 0.1 $\mu g \cdot ml^{-1}$, respectively.

Discussion: Use of a propofol infusion was effective in maintaining hemodynamic stability during cardiac anesthesia. Compared to the pre-CPB period, higher infusion rates were required during CPB to achieve effective (therapeutic) propofol levels. Interestingly, the mean effective propofol concentrations did not differ during the pre-CPB and CPB periods. These propofol concentrations are similar to the therapeutic levels required during major intra-abdominal surgery with a propofol-nitrous oxide-relaxant technique (4). The arterial-venous differences during CPB presumably reflect the fact that the propofol infusion was administered directly into the bypass machine. Higher mixed venous (vs arterial) concentrations before and after CPB would suggest that propofol may be sequestered (or eliminated) in the pulmonary circulation. Further studies are needed to determine the disposition of propofol during cardiac anesthesia.

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Title: ESTIMATION OF MEAN LEFT ATRIAL PRESSURE BY TRANSESOPHAGEAL PULSED DOPPLER OF PULMONARY VENOUS FLOW.

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Introduction: Intraoperative transesophageal echocardiography is a useful method for evaluation of regional wall motion abnormalities and intravascular volume status (1-2). However it has not been used for estimation of intracardiac pressures. Pulmonary venous flow has been shown to directly relate to left atrial pressure (3-4). Therefore, we studied pulmonary venous flow patterns using pulsed Doppler intraoperatively to determine whether these flow patterns relate to mean left atrial pressure.

Methods: The study protocol was approved by the Committee on Human Research at the University of California, San Francisco. We studied 26 patients (age 34-77 years) undergoing cardiovascular surgery (CABG, n=23, AVR, n=3). Mean left atrial pressure was measured either by using a left atrial line or by pulmonary capillary wedge pressure. Doppler tracings of pulmonary venous flow were recorded simultaneously by a blinded observer. From these tracings we measured peak and integrated flow velocities. Exclusion criteria were mitral regurgitation, hemodynamic instability, atrioventricular block, paced rhythms or technically inadequate Doppler tracings.

Results: Left atrial pressure was derived from pulmonary capillary wedge pressure in 34 episodes, and from a left atrial catheter in 21 episodes. High levels of mean left atrial (>15mmHg) decreased peak systolic and increased peak early diastolic flow velocity. Of all Doppler variables studied the systolic velocity-time integral as a fraction of the total velocity-time integral correlated closest with various levels of mean left atrial pressure (r=-0.86) (Fig 1). In individual patients, changes in this fractional systolic velocity time integral correlated well with changes in mean left atrial pressure (r=0.79) (fig2).

Discussion: The results of this study show that pulmonary venous flow patterns are significantly related to mean atrial pressure. As the left atrial pressure rises the pulmonary venous flow patterns show a shift from systolic to early diastolic forward flow predominance, and as the pressure decreases the pattern reverts towards normal. We conclude that transesophageal pulsed Doppler of pulmonary venous flow offers a rapid and reliable means of semiquantitative assessment of mean atrial pressure.

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Figure 1: Various Levels of Mean Left Atrial Pressure and Pulmonary Venous Flow

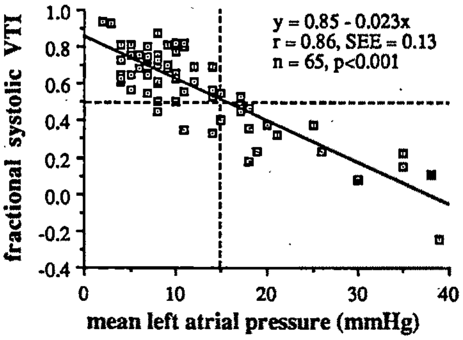
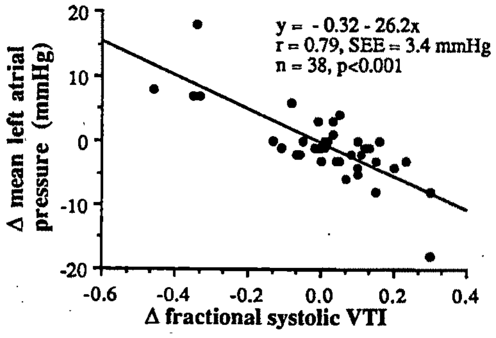


Figure 2: Changes in Mean Left Atrial Pressure and Pulmonary Venous Flow



TITLE: HYPOXIC VASOCONSTRICTION IN ISOLATED AORTIC VASCULAR SMOOTH MUSCLE CELLS: THE ROLE OF MUSCLE IN HPV

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INTRODUCTION: Decreases in oxygen partial pressure in the lungs can initiate narrowing of pulmonary vessels by a process known as hypoxic pulmonary vasoconstriction. This is a prominent active process for matching ventilation and perfusion by shunting blood away from diseased or poorly ventilated lung regions and towards regions with better capacities for gas exchange. This property appears to be unique for pulmonary vessels, in that the typical response to hypoxia in systemic vessels is one of vasodilation. From a teleologic point of view, it is apparent why hypoxic vasoconstriction is beneficial in an atelectic lung segment but that systemic vasodilation would be preferable when blood PO_2 is lowered in those vessels. However, an explanation for the paradoxical response in these two vascular beds has yet to be demonstrated. Much of the reason for this undoubtedly lies in the fact that the cellular mechanism by which hypoxia is sensed by pulmonary tissue is not understood. Nor is it known how this is transduced into contraction of the vascular smooth muscle (VSM) within the vessel. Recent work aimed at determining the site in the vessel wall for sensing hypoxia by independently varying the alveolar and mixed venous PO_2s showed that vessels behaved as though the sensor was located in the muscular portion (1). Also, cultures of pulmonary artery VSM cells devoid of endothelial contamination were shown to demonstrate contractile responses to hypoxia (2). This indicated that pulmonary VSM cells were capable of sensing hypoxia and constricting to it in the absence of any other components of the vessel wall. The present studies were aimed at establishing the response of isolated aortic VSM cells to hypoxia in an effort to determine whether the paradoxical response of pulmonary vs aortic vessels is due to intrinsic properties of the muscle itself or due to non-muscle factors (such as endothelial-derived products).

METHODS: Cultures of bovine aortic VSM cells were established, fed twice weekly with Medium 199 plus 10% fetal bovine serum and passaged at weekly intervals. Changes in cell tension in response to hypoxia were observed using the method of Harris (3) as previously described (2). Microscope cover slips were coated with a thin layer of silicone fluid (polydimethyl siloxane, 30,000 centistokes in viscosity). Cover slips were then inverted and heated over a low flame which caused polymerization of the silicone surface while leaving the underlying material as a viscous fluid. Isolated aortic VSM cells were then inocculated onto these preparations. Changes in tension forces generated by the cells in response to changes in PO_2 were observed as elastic distortions and wrinkles in the polymerized growth surface. These were readily apparent under phase-contrast microscopy. Aortic VSM cells were photographed at various times before, during, and after exposure to an hypoxic atmosphere (PO_2 20-30 mmHg).

RESULTS: Cultured bovine aortic VSM cells exhibited some basal tension forces when maintained under standard culture conditions (as shown by wrinkling seen in Figure 1A). Exposure of these same cells to an hypoxic atmosphere for 5 minutes brought about a marked increase in the wrinkling of the silicon under some cells indicating an increase in cell tension (Figure 1B). Contractile responses of this type were noted in 10 of 12 cultures tested for periods ranging from 1-30 minutes of hypoxia. Cells subcultured up to 5 times and maintained in culture up to 7 weeks continued to show hypoxic contractions. Distortions of the surface were noted to decrease upon resumption of normoxia in some cases.

DISCUSSION: Contraction of isolated pulmonary VSM cells to hypoxia in the absence of other cells types has been reported previously (2). The present work shows that isolated aortic VSM cells will also contract to hypoxia, unlike intact systemic vessels which dilate with low PO_2. This paradoxical response of the isolated aortic VSM suggests that the muscle cells from pulmonary and systemic vascular beds may not be fundamentally different. Rather, the vasodilation to hypoxia in systemic vessels may be mediated by other factors in those vessels, such as endothelial-derived substances.

Supported in part by grants from Pennsylvania Thoracic Society and NIH GM5T30276

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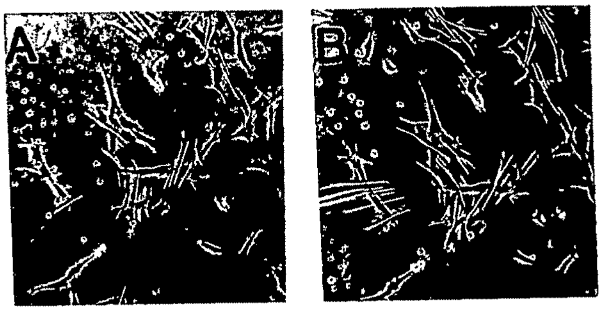
FIGURE 1. Contraction of aortic VSM cells to hypoxia



Title: **HALOTHANE ATTENUATES REACTIVE OXYGEN INTERMEDIATES' IMPAIRMENT OF CANINE VASCULAR FUNCTION**

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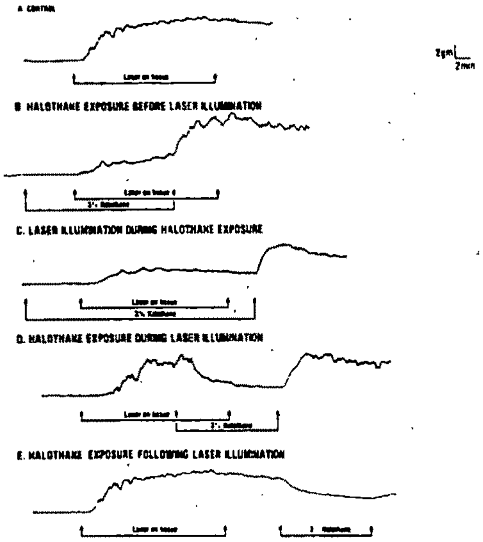
Introduction Oxygen radicals and reactive oxygen intermediates (ROIs) have been implicated concerning various pathologic and physiologic effects on vascular function. Elevated ROI production is linked with impaired vascular function in selected pathologic states[1]. Volatile anesthetics (including halothane) reportedly have a role in minimizing damage during reperfusion injury[2]. The objective of this study is to determine if halothane could attenuate the effects of ROIs on vascular function.

Methods This study was approved by the Institutional Laboratory Animal Use Board. Isolated canine saphenous veins were suspended in aerated Krebs-Ringer bicarbonate solution (37°C) for isometric tension recording. ROIs were produced by laser illumination of photosensitizer (hematoporphyrin derivative, HpD) pretreated tissue. The vascular rings were incubated with photosensitizer for 30 min (3ug/ml) and washed in fresh Krebs solution before laser illumination using a Melles-Groit helium-neon laser(632.8 nm, 1.5-3mW intensity). Halothane was delivered in 1 to 3% concentrations from calibrated vaporizers monitored by an infrared halothane analyzer (Sensor Medics, Model LB-2, Anaheim,CA). Analysis of data was performed using a blocked multi-way analysis of variance. A probability level of less than 0.05 was considered significant.

Results Reactive Oxygen Intermediates (ROI), produced during laser illumination of HpD pretreated canine saphenous vein, evoked a sustained contraction (Fig. 1A). If halothane preceded laser illumination, significant attenuation of ROI induced contraction was observed. However, tissue continued to contract after the halothane was discontinued regardless of whether the laser illumination was present (Fig. 1B) or not (Fig. 1C). Pre-existing laser generated contractions could be opposed in the presence of halothane and return after the halothane was turned off (Fig. 1D). This relaxation property of halothane was evident even if halothane was applied 10 minutes after termination of laser illumination (Fig. 1E). In another experiment, ROI induced contractions (initial contractions) promptly relaxed in the presence of calcium free solutions. When the calcium was incrementally added back to the bathing solution 30 min later, the contraction returned in a parallel manner with rising calcium concentration (delayed calcium dependent contraction). Halothane (3% conc.) significantly attenuated the delayed calcium dependent increase in tension. The initial contraction could be blocked by oxygen scavengers and reduced by calcium free solutions. The delayed contraction could be eliminated by calcium free solutions, significantly attenuated by calcium channel blockers, and remain unaffected by radical scavengers.

Discussion Reactive oxygen intermediates are constantly produced and scavenged by normal healthy cells. Production of ROIs change vascular smooth muscle membrane permeability to calcium for a prolonged time. A contraction of vascular smooth muscle is observed when ROIs are produced and 30 min later upon return of calcium when ROIs are not being produced. By comparing the actions of halothane on these two types of contractions, we found halothane's action unlike scavengers and antioxidants (catalase and ascorbate) and more similar to calcium channel blockers, suggesting halothane's effect during ROI vascular interaction is likely due to its effect on membrane calcium permeability.

INTERACTION OF HALOTHANE & LASER ILLUMINATION ON HPD PRE TREATED BLOOD VESSELS



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INFLUENCE OF TOURNIQUET DEFLATION ON CARDIAC OUTPUT AND OTHER CARDIOPULMONARY VALUES DURING LOWER EXTREMITY SURGERY

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INTRODUCTION: Arterial hypertension induced by tourniquet inflation during orthopedic surgery has been reported with general anesthesia (1). However, severe hypotension may occasionally result on deflation of the tourniquet. Acute increase in end-tidal CO_2 reported following release of the tourniquet might decrease cardiac contractility (2) and also increase pulmonary vascular resistance. Therefore this increased $PaCO_2$ may have a significant impact on trauma patients especially with contusion of the heart. The technique of thoracic electrical bioimpedance offers continuous non-invasive measurement of cardiac output. The purpose of this study is to investigate the influence of tourniquet deflation on cardiac output and other cardiopulmonary values during lower extremity surgery.

METHODS: This study was approved by the institutional review committee. Nine patients undergoing lower extremity surgery with tourniquet placement under general anesthesia were studied. Anesthesia was induced with sodium thiopental (3-4mg/Kg) and fentanyl (2-3μg/Kg) and intubation was facilitated with the use of vecuronium (1mg/Kg). Anesthesia was maintained with additional doses of fentanyl, isoflurane and nitrous oxide in oxygen. Each patient was monitored with ECG, automated blood pressure cuff, pulse oximetry, capnometry and thoracic electrical bioimpedance (TEB). Hemodynamic data, cardiac output (CO), systolic blood pressure (SBP), heart rate (HR), and end-tidal CO_2 ($ETpCO_2$) were documented in the following stages: before tourniquet deflation, and 1, 3 and 5 minutes after tourniquet deflation. Arterial blood gas values were also obtained before tourniquet deflation and within 3 minutes of tourniquet deflation. Results were analyzed with paired t-test and simple regression. P value < 0.05 is considered statistically significant. Results are expressed as mean ± standard deviation.

RESULTS: Results were summarized in Tables 1 and 2. Cardiac output was significantly increased at one minute and five minutes following tourniquet deflation ($p < 0.05$). However, there were no significant differences in systolic blood pressure (SBP) and heart rate (HR) before and after tourniquet deflation. End-tidal CO_2 ($ETpCO_2$) was significantly increased at all stages after tourniquet deflation when compared to $ETpCO_2$ before tourniquet deflation ($p < 0.05$). Arterial blood gas analysis showed significant increases in $PaCO_2$ as well as significant decreases in PaO_2 and pH ($p < 0.05$). However no significant changes in K+ were seen. There were no correlations between tourniquet time and changes in CO, CBP, HR, $ETpCO_2$, and arterial blood gas values.

DISCUSSION: This study demonstrated that cardiac output increased immediately after the release of the tourniquet during lower extremity surgery despite no significant changes in systolic blood pressure and heart rate. This study has also confirmed a previous report documenting significant increase in $PaCO_2$ and $ETpCO_2$ following the release of extremity tourniquet (3). This significant increase in $PaCO_2$ and significant decrease in PaO_2 despite increase in cardiac output may have a significant impact on the management of trauma patients who have concomitant head injury or chest injury while repairing lower extremities with the use of tourniquet. We recommend close observation in trauma patients with pulse oximetry and capnometry at the time of tourniquet deflation.

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TABLE 1 TOURNIQUET STUDY

	On T	Off T 1 min	Off T 3 min	Off T 5 min
CO l/min	6.3±2.7	7.0±2.8*	6.7±2.6	7.1±2.4*
SBP mmHg	119±11	117±11	119±13	120±10
HR /min	68±19	76±18	67±13	66±11
$ETpCO_2$ mmHg	32.4±4.6	40.3±7.2*	40.2±9.7*	38.5±7.5*

T = tourniquet
Data are means ± SD
*$p < 0.05$ - statistically significant

TABLE 2 TOURNIQUET STUDY ON ARTERIAL BLOOD GAS

Stages	On T	Off T
pH	7.40 ± 0.06	7.35 ± 0.05*
$PaCO_2$ mmHg	37.3 ± 7.4	42.5 ± 9.4 *
PaO_2 mmHg	222 ± 89	174 ± 80*
K+ meg	3.6 ± 0.2	3.7 ± 0.4

T = tourniquet
Data are means ± SD
*$p < 0.05$ statistically significant

Title: Portable Percutaneous Cardiopulmonary Bypass: Prophylactic and Therapeutic Uses

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Introduction: Conventional circulatory support systems, such as the intra-aortic balloon pump, have achieved widespread use due to their effectiveness and ease of application.[1] Supportive veno-arterial cardiopulmonary bypass (CPB) via surgical exposure of the femoral artery and vein is a proven technique.[2] Recently percutaneous (CPB) systems have become available. This abstract reflects our experience with the Bard Cardiopulmonary Support System (CPS) used as an adjunct to the performance of complex coronary angioplasties (A) and valvotomies (V) and as a temporary full cardiopulmonary support system in the cardiac arrest (CA) situation.

Methods: Six patients undergoing elective high risk A (n=4) or V (n=2) gave their informed consent to the institutionally approved protocol. An additional 20 patients who suffered CA and placed on CPS are also included. The Bard CPS system is a device consisting of a biomedicus centrifugal blood pump, a hollow fiber membrane oxygenator, a normothermic electric heat exchanger, one 15cm femoral artery cannula and one multiorifice 65cm femoral venous cannula which may be inserted percutaneously or via surgical cutdown. All patients were given heparin 3mg/kg prior to the institution of CPB. The patients who had A or V were placed on CPB prophylactically prior to the beginning of the procedure. Flow rates, perfusion pressures, metabolic and acid base status were optimized in each patient. The CPS system provided flows of 3.5-4.0 L/mn in all patients. All patients were given O_2 via a face mask and were monitored with leads II and V5 of the EKG, pulmonary arterial catheters, systemic arterial catheters, and a pulse oximeter. The 20 patients who suffered CA were placed on emergency CPB after conventional ACLS methods were exhausted and were subsequently taken to the cath lab or operating room if deemed appropriate.

Results: All 6 patients who underwent elective A or V were discharged from the hospital in satisfactory condition. Neosynephrine boluses were required in several patients to maintain satisfactory coronary and cerebral perfusion pressures. There were no complications.

Of the 20 patients who suffered CA, 7 occurred in the cardiac cath lab, 6 in the SICU after cardiac surgery, and 7 in other hospital locations. CPS was successful in restoring satisfactory hemodynamics and cardiac rhythm in all patients. Four of the 7 patients who arrested in the cath lab were taken to the OR and one was discharged from the hospital. Three of the 6 patients who arrested on the floor were short term survivors and 2 were discharged from the hospital. One out of the six of the patients who arrested in the SICU was a long-time survivor. The following case presentations are representative of our experience.

Case 1. An 8 year old, 40 kg female suffered a CA 2 days after the acute onset of viral myocarditis. After multiple attempts at resuscitation she was placed on CPS. Initial echocardiographic estimation of ejection fraction was 12%. Several days later her EF increased to 50% and the CPS system was successfully removed.

Case 2. A 71 year old male with a history of multiple myocardial infarctions associated with CHF requiring intubation presented for angioplasty of a 95% LAD lesion. His EF was 23% and he had a large LV aneurysm. He underwent successful dilation of the LAD while on prophylactic CPS and was discharged 3 days later.

Case 3. A 65 year old male S/P CABG and angioplasty underwent an uneventful redo CABGx4. Several hours later he required increasing inotropic support and eventually had a CA. He was placed on CPS in the ICU and take back to the OR where he underwent regrafting of his acute marginal lesion. He was discharged from the hospital one week later in good condition.

Discussion: The Bard CPS system provided satisfactory full temporary circulatory support in the CA situation as evidenced by the restoration of stable hemodynamics and EKG. Unlike earlier cumbersome systems consisting of roller pumps, bubble oxygenators and gravity venous drainage which often resulted in inadequate flows, venous blood is actively aspirated from the right atrium with this system which facilitates higher flow rates. Consequently, central line placement is relatively contraindicated once CPS has begun in order to reduce the incidence of air emboli. In addition, to maintaining normal metabolic and acid base status, it is important to ensure adequate coronary and cerebral perfusion pressures especially in the absence of hypothermia. CPB, however, is not innocuous and the indications for the appropriate use of prophylactic CPS are continuing to evolve. Since all of the A and V were uneventful, perhaps the prophylactic placement of guide wires into the femoral artery and vein may have been sufficient. In selected cases of refractory CA, emergent CPB may be a lifesaving maneuver that buystime for diagnostic and therapeutic intervention.

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ACRYLATE METABOLITES OF ATRACURIUM AS THE PROXIMATE CYTOTOXIC AGENT IN CULTURED RAT HEPATOCYTES

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INTRODUCTION

We tested the working hypothesis that acrylates, a product of Hofmann elimination of atracurium (ATR), are responsible for the cytotoxic effect observed in isolated rat hepatocytes exposed to ATR. The experiments were designed to measure the cytotoxicity of acrylates as modified by interventions known either to abolish the electrophilic nature of acrylates or to retard the detoxification of acrylates in the cells. As a working hypothesis we postulated that the cytotoxicity will be augmented when the intracellular detoxification of acrylates is retarded and, conversely, the cytotoxicity will be abolished when the chemical reactivity of acrylates is saturated by a nucleophile, or acrylates hydrolyzed to a much weaker electrophile acrylic acid, prior to the exposure to the hepatocytes.

METHODS

Primary cultures of rat hepatocytes were prepared as described.[1] Leakage of lactate dehydrogenase (LDH) from the cells into the incubation medium, after a 4-hour incubation with ATR products, was used to quantify the toxicity. The leakage of LDH was expressed in percent of the total intracellular LDH. In all experiments, ATR (0 to 0.8 mM) was allowed to decompose spontaneously at pH 8.0 at 37°C for 120 min. Subsequently, acrylate esters formed during this time were either converted to cysteine adducts (by the addition of cysteine, 3mM) or hydrolyzed to acrylic acid (by carboxylesterase, CE, 1.6 U/mL). The products formed (a) after ATR degradation, (b) after the addition of cysteine, or (c) after hydrolysis with CE, were incubated with hepatocytes for 4 hours. Detoxification of acrylates in the hepatocytes was inhibited by the treatment of cells for 24 hours prior to the exposure to ATR products. This consisted of exposure to buthionine sulfoximine (BSO, 0.009 mM) and/or to bis-p-(nitrophenyl) phosphate (BNPP, 0.0028 mM). BSO is an inhibitor of gama-glutamylcysteine synthetase and reduces the rate of synthesis and the intracellular concentration of glutathione (GSH). BNPP is an inhibitor of CE. Both BSO and BNPP are specific and irreversible inhibitors of the respective enzymes.

RESULTS

The results demonstrated: 1) A marked cytotoxicity of the products of ATR degradation; 2) No toxicity to the hepatocytes if the products were initially combined with cysteine or hydrolyzed by CE; 3) A highly increased toxicity of ATR products to hepatocytes in which the detoxification of acrylates was attenuated (pretreatment with BSO and/or BNPP); 4) No toxicity when the hepatocytes treated with BSO and/or BNPP were exposed to the products that were previously combined with cysteine or hydrolyzed by CE.

DISCUSSION

Leakage of LDH from the hepatocytes results from the destruction of the incubated cells. The extent of leakage is proportional to the fraction of lethally injured cells. The phenomenon and its interpretation are analogous to the clinical use of elevated enzymes in plasma of patients with massive tissue necrosis (myocardial infarction, hepatitis, muscle injury after a bout of malignant hyperthermia, etc.)

Our results are compatible with the working hypothesis that the spontaneous degradation of ATR (i.e., Hofmann elimination) generates acrylates and that these electophilic metabolites produce cell death by alkylating endogenous nucleophiles. Inhibition of one or of both intracellular detoxification routes of acrylates, viz., conjugation of acrylates with GSH and/or their hydrolysis by CE, enhances the probability of acrylates alkylating the functionally important nucleophiles. More extensive alkylation thus augments toxicity. Since these results demonstrate that the detoxification of acrylates occurs intracellularly, they imply that acrylate metabolites of ATR diffuse across the plasma membrane of hepatocytes and distribute in the intracellular space.

In additional experiments, the intracellular detoxification of acrylates was mimicked in vitro prior to the contact with the hepatocytes. Cysteine was used instead of the nucleophile GSH to produce cysteine-acrylate adducts; hydrolysis of acrylates to acrylic acid was accomplished by the incubation of ATR degradation products with CE. Exposure of the hepatocytes to the detoxified products of ATR degradation was, therefore, not expected to cause toxicity. This postulate was confirmed, since no toxicity was observed either in normal hepatocytes or in the hepatocytes pretreated with BSO and/or BNPP. Furthermore these experiments permit us to exclude laudanosine, also a product of Hofmann elimination, as the agent responsible for cytotoxicity.

We conclude that electrophilic acrylate metabolites of ATR reach and alkylate intracellular nucleophiles. In agreement with the conclusions of other investigators with different reactive compounds, we propose that alkylation of the endogenous nucleophiles by acrylates is followed by cell death if the amount of the reactive metabolites overwhelms the cellular defense mechanisms.

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ACKNOWLEDGEMENT

B. B. Sankey Anesthesia Advancement Award by IARS is gratefully appreciated.

TITLE: RESPIRATORY AND MOTOR FUNCTION DURING BUPIVACAINE SPINAL ANESTHESIA FOR CESAREAN SECTION

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Introduction: In parturients, high levels of sensory blockade frequently occur following subarachnoid injection of 15 mg hyperbaric bupivacaine(1). Such high levels of local anesthetic blockade could cause significant motor and respiratory impairment and place patients at increased risk of gastric acid aspiration(2). The purpose of this study was to evaluate the motor and respiratory consequences of 15 mg subarachnoid bupivacaine in the parturient.

Methods: The Institutional Review Board approved our protocol; 12 healthy term parturients presenting for nonemergent cesarean section under spinal anesthesia consented to participate. With the women in the right lateral decubitus position, we induced anesthesia by injecting 15 mg 0.75% bupivacaine with 8.25% dextrose and 0.15 mg morphine into the subarachnoid space via a 25 g needle at the L2-3 or L3-4 interspace. The subjects were then placed supine with a wedge under the right hip. Intravenous fluids and ephedrine were administered as clinically indicated.

Upper extremity muscle strength was measured with a hydraulic hand dynamometer (Therapeutic Instruments, Clifton, N.J.) before and 15 minutes after induction of anesthesia. For both measurements, the women lay supine with their arms abducted to 90°. The best effort of 3 trials was used for statistical analysis.

Respiratory function was measured before and 15 minutes after induction of anesthesia using a pneumotach portable spirometer (Spiromate AS-600, Riko Medical Scientific Instrument Corp.). Before each study the spirometer was calibrated with a 3 l syringe and corrected for temperature, humidity and barometric pressure. At each time the women performed repeated trials until 2 trials produced results within 5%. The better of these 2 trials was accepted for statistical analysis.

The dominant and nondominant hand grip strength and the FVC, FEV$_1$, PEFR, and FEF$_{25-75}$ values obtained before and after spinal anesthesia were compared using paired Student's t-test. All values are reported as mean ± SEM, and $p<0.05$ was considered significant.

Results: The 12 subjects were 29.6 ± 1.2 yrs old, 164.6 ± 1.7 cms tall and weighed 87.1 ± 3.6 kg. Sensory blockade ranged from T3 to C3, with all blocks adequate for cesarean section. Hand grip strength decreased 13 - 18% in both dominant and nondominant hands(figure 1). Respiratory function decreased after blockade, significantly impairing all flow measurements(figure 2). PEFR decreased by 22.6 ± 2.0% and fell below 3.3 l/s in 2 patients (3.1, 2.9 l/s). There was no correlation between the extent of sensory blockade and the degree of motor or respiratory impairment.

FIGURE 1: HAND GRIP STRENGTH BEFORE AND AFTER SPINAL BLOCKADE WITH BUPIVACAINE

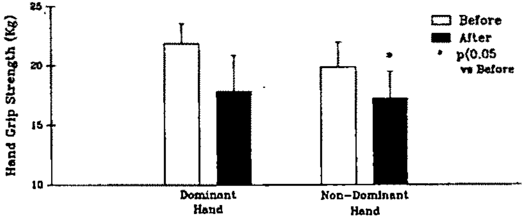
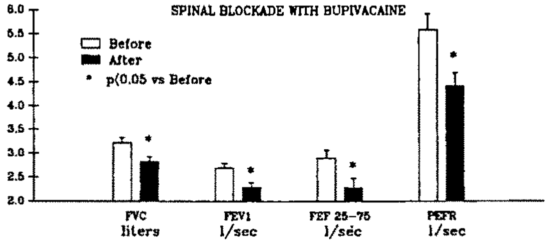


FIGURE 2: PULMONARY FUNCTION BEFORE AND AFTER SPINAL BLOCKADE WITH BUPIVACAINE



Discussion: High thoracic levels of sensory blockade associated with spinal anesthesia have little effect on resting ventilatory exchange or inspiratory function. Such levels have been reported to diminish forced expiratory flow rates, probably by abolishing abdominal muscle tone and limiting the patient's ability to increase intra-abdominal pressure(3). This restriction can significantly impair the ability to cough and may increase the risk of aspirating regurgitated gastric contents(4). Gamil warns that PEFR below 3.3 l/s may be associated with inability to perform an adequate cough(2). Two of our subjects fell below this threshold.

In summary, while spinal anesthesia for cesarean section with 15 mg 0.75% bupivacaine only minimally impairs motor and respiratory function, occasional women may suffer significant respiratory compromise which may impede their ability to cough and protect their airway.

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Title: Mechanism of Vasodilator Actions of Cromakalim in the Pulmonary Vascular System of the Cat.

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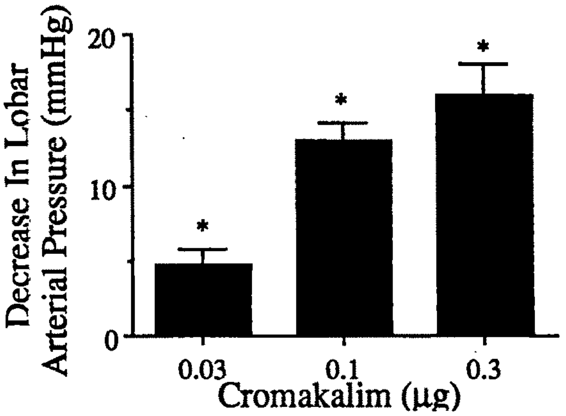
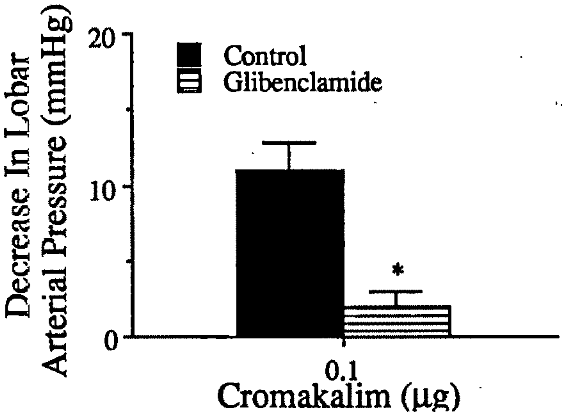
Introduction: Cromakalim is a new and novel orally effective antihypertensive agent. However, the actions of cromakalim which enhances potassium permeability in vascular smooth muscle on the pulmonary vascular bed are uncertain. In the present study, we investigated the mechanism of action of cromakalim in the pulmonary vascular bed of the cat. Cromakalim is one of a new series of benzypryan derivatives being developed as an antihypertensive drug. Peripheral vasodilation through its relaxant actions on vascular muscle is the mechanism of its antihypertensive effect.[1, 2] Evidence from electrophysiological studies in cultured aortic smooth muscle cells confirms the ability of cromakalim to open potassium (K^+) channels at the single channel level.[3] *In vitro* profile of action shows distinct differences from other vasodilator drugs such as hydralazine[4] and calcium (Ca^{2+}) channel antagonists such as nifedipine.[4, 5] The hyperpolarization that results from this K^+ channel activation by cromakalim is likely to oppose the entry of Ca^{2+} into the smooth muscle cells through voltage-dependent Ca^{2+} channels, and to inhibit the activation of those cells responsible for generating tone in vascular tissue. Glibenclamide, a new hypoglycemic agent, has been shown to inhibit the actions of cromakalim by blocking the ATP regulated potassium (K^+) channel.[6] In the presence of glibenclamide, pulmonary vascular resistance responses to cromakalim will again be compared.

Methods: This research was approved by the institutional animal investigation committee. For studies on the nature of cromakalim responses in the feline pulmonary vascular bed under conditions of controlled pulmonary blood flow and constant left atrial pressure, adult cats unselected as to sex were sedated with ketamine hydrochloride, 10-15 mg/kg IM, and were anesthetized with pentobarbital sodium, 30 mg/kg IV. The animals breathed room air enriched with oxygen. Systemic arterial pressure was measured from the aorta. For perfusion of the hemodynamically separated left lower lung lobe, a specially designed 6F triple lumen balloon-perfusion catheter was passed under fluoroscopic guidance from the left external jugular vein and into the pulmonary artery of the left lower lobe. After the animals are heparinized, 1000 U/kg IV, the lobar artery is isolated by distension of the balloon cuff on the catheter. The lung was perfused through a catheter port immediately beyond the balloon cuff, with blood withdrawn from a femoral artery with a Harvard model 1210 peristaltic pump. The flow rates range between 40-55 ml/min. Left atrial pressure is measured by means of another 4F catheter passed transseptally under fluoroscopic guidance into the vein draining the left lower lobe. All vascular pressures are measured with Gould P-23ID transducers zeroed at right atrial level, and mean pressures obtained by electronic averaging are recorded on a Grass model 7 recorder.

Results: Injections of cromakalim during the control period into the perfused lobar artery caused dose related decreases in lobar arterial pressure. After administration of glibenclamide, the reduction in response to cromakalim was greater than 95%.





Discussion: These results indicate that cromokalim has significant vasodilator activity in the pulmnary vascular system of the cat and its mechanism of action could be dependent upon K^+ channel stimulation. Cromakalim is a member of a new class of agents which may be useful as a vasodilator in those clinical conditions in which pulmonary vascular resistance is high.

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Title: PROTAMINE-HEPARIN INDUCED PULMONARY HYPERTENSION: TREATMENT WITH A THROMBOXANE A_2 RECEPTOR ANTAGONIST IN PIG

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Introduction. Protamine reversal of heparin is often associated with severe hemodynamic side effects. One adverse reaction that can occur is pulmonary hypertension and right heart failure, thought to be mediated by thromboxane A_2. Pretreatment with a thromboxane A_2 receptor antagonist prevents protamine-heparin complex induced pulmonary hypertension in pigs (1). The current study was designed to assess the effect of post-treatment thromboxane A_2 antagonism in protamine-heparin induced pulmonary hypertension. In addition the thromboxane A_2 receptor blocker's effect on platelet aggregation, PT, APTT, and its effect on bleeding time was also studied.

Methods. Following approval from our Institutional Animal Care and Use Committee, under 1 MAC halothane anesthesia two groups of pigs were studied: a control group (N=9) which received i.v. heparin (300 IU/kg) followed after 10 min by a heparin neutralizing dose of protamine (3 mg/kg); and a treatment group (N=11) which was identical except that thromboxane A_2 receptor antagonist, L-670596 (Merck-Frosst, Canada) (1 mg/kg), was infused 2 min following the protamine. Pulmonary arterial, wedge, right atrial, systemic arterial, and left ventricular (LV) pressures were measured. Left ventricular dP/dt was derived from a differentiator of LV pressure. Cardiac output was calculated by thermodilution technique. From the above data, pulmonary vascular resistence (PVR) and systemic vascular resistence (SVR) were calculated. Blood was drawn for coagulation studies before heparin, post-heparin, post-protamine, and post-antagonist. The coagulation studies included platelet aggregation studies (to adenosine diphosphate (ADP), collagen, and arachidonic acid stimulation), complete blood count, prothrombin time, activated partial thromboplastin time, and activated coagulation time. Blood was also drawn at the above time points for determination of thromboxane plasma levels by a radioimmunoassay technique. Bleeding times were measured by the Mertz modification of the Doetl and Ripke technique (2) before heparin, 1 min post-protamine, 1 min post-antagonist, and 12 min post-antagonist. The time interval from peak of pulmonary arterial hypertension following protamine administration, to return to baseline mean pulmonary arterial pressure was determined by a blinded observer.

Results. We found that in all the pigs protamine-heparin-complex mediated pulmonary hypertension developed within 2 min and reached a peak within 2-5 min following the administration of protamine. PVR increased in a similar pattern. Treatment with the thromboxane A_2 receptor antagonist, L-670596, 2 min following the protamine, significantly attenuated the duration and degrees of pulmonary hypertension. The mean time interval for return of mean pulmonary artery pressure from peak to baseline values was 11.6 vs. 5.5 min for control and treatment groups, respectively ($P<0.01$) (Fig.1). dP/dT decreased 20% with protamine administration, rapidly returning to baseline values, and was unaffected by the administration of L-670596. There was no difference between thromboxane B_2 plasma levels which increased following protamine administration in both groups. There was a linear relationship between thronboxane B_2 levels and the pulmonary hypertension ($R=0.56$, $P<0.05$). Platelet aggregation to ADP and arachidonate was not affected by heparin, protamine or the thromboxane antagonist. Platelet aggregation to collagen was inhibited by heparin and protamine, and further inhibited by L-670596 ($P<0.05$). Bleeding time was prolonged beyond normal range in 50% of L-670596 treated pigs, but was almost back to baseline by 12 min (Fig. 2).

Discussion. This study corroborates previous reports that the pulmonary hypertension following protamine reversal of heparin is thromboxane mediated. The important outcome of this study, however, was that the pulmonary hypertension could be attenuated by post-hoc administration of the thromboxane receptor antagonist. It should be noted that 50% of the pigs had a normal bleeding time after treatment with the antagonist, and in the 50% of pigs with a prolonged bleeding time, improvement was noted by 12 min. These results have important implications for the future management of patients developing pulmonary hypertension following cardiopulmonary bypass.

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FIGURE 1.

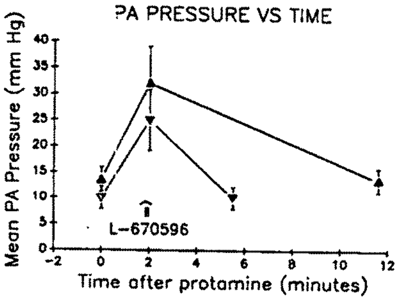
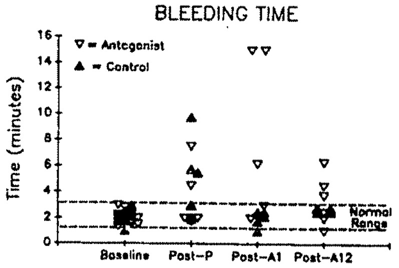


FIGURE 2.



TITLE:

AN EPIDEMIC OF HEADACHE AFTER SPINAL ANESTHESIA?

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Introduction In early 1989 some surgeons and nurses at hospital A formed an impression that an excessive number of patients who had spinal anesthesia developed postoperative headache. Their concerns led the Chief of Surgery to ask the Department of Anesthesia about post-spinal headaches. The subsequent investigation revealed some new insights.

Methods In 1988-89, prospective assessments of postoperative morbidities were occurring in hospitals A and B. After approval from the University Ethics Committee, 6439 patients from hospital A and 2473 patients form hospital B were interviewed after anesthesia and surgery by a research nurse. Patients were directly asked if they had any new symptoms, including headache, after surgery. For patients responding positively, the severity of their headaches, was assessed by a 5-point visual analogue scale. Subsequently, patients' hospital charts were reviewed and the presence or absence of headache in the chart was noted. We compared the results from hospital A to those from hospital B. We evaluated the incidences of headache among subgroups of patients stratified on the basis of age, sex, physical status, and anesthetic technique. We compared the incidences of headache as reported by patients and by hospital charts. The data were analyzed by chi-square analysis and $P<0.05$ was considered significant.

Results The overall incidence of postoperative headache was higher at hospital B than hospital A (17.3% vs 9.0% P 0.001). However, there was no difference in the incidence of severe headache (score of 3 or more on the visual analogue scale) among patients from the two hospitals (B:3.1% vs A:3.5%). In both hospitals, female patients had higher incidences of headaches than male patients ($P<.01$). Female patients had significantly higher rate of severe headache also. At both hospitals, the overall incidences of headache among patients who recieved spinal anesthetics were higher than patients who received other regional anesthesia or monitored care (Table 1). Incidences of postoperative headache are similar after general and spinal anesthesia. But, the incidences of severe headache are similar among all patients who received different anesthetics. At hospital A, patients with physical status 1 or 2 had more headaches ($P<0.001$). Older patients were less likely to report headaches ($P<0.05$). At hospital B, there was a trend for decreasing rate of headache with older patients but the difference was not statistically significant ($P=0.065$).

For 83.5% of the patients who reported headache, there was no note of headache in their charts. For 11% of the patients who reported no headache, headache was recorded in those patients' charts.

Discussion We have found that headaches are common among patients in the postoperative period regardless of the anesthetic technique. Female patients, younger patients and patients who had spinal anesthesia had higher rates of postoperative headache. These results are consistent with some previous studies.[1,2] In addition, we showed that the rate of severe headache were similar among patients who received different anesthetics. We also showed that headaches are less frequent in patients with poor physical status.

The rate of headaches in response to direct questioning was significantly higher than that recorded in the patients' charts. Therefore, if physicians and nurses are selective in questioning certain patients about headache, the results would be skewed. Although hospital A had a lower incidence of postoperative headache than hospital B, the staff of hospital A had more concerns.

As more and more hospitals institute quality assurance activities, we must pay close attention to the methods used to gather and interpret those data. Uncontrolled abstractions of data from charts and incident reports may provide false impressions. In studies of subjective symptoms, such as headache, the structured interview with proper control groups would be more appropriate.

In summary, our data indicate that many patients have postoperative headaches. Besides anesthetic technique, patients' sex, age, and physical status can affect the incidences of postoperative headache. Patients who had spinal and general anesthesia have similar incidences of postoperative headache. Spinal anesthesia should not be excluded by excessive concerns about postoperative headache.

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TABLE 1. Incidence of postoperative headache after different anesthetic techniques at hospital A.

Anesthetic Technique	All Headaches	Severe Headaches
	(% of patients who had such anesthetics)	
GENERAL	9.4%	3.6%
SPINAL	10.3%*	5.0%
OTHER REGIONAL	5.2%	2.4%
MONITORED CARE	8.2%	2.8%

* $P<0.05$

Title: HEMODYNAMIC RESPONSES TO ISOFLURANE, SODIUM NITROPRUSSIDE AND ESMOLOL INDUCED HYPOTENSION

Authors: E Ornstein, PhD, MD; WL Young, MD; N Ostapkovich, REEGT; RS Matteo, MD; J Diaz
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INTRODUCTION: In a randomized controlled study, esmolol has been shown to be a safe and effective primary agent for the induction of deliberate hypotension.[1] In comparison to sodium nitroprusside (SNP), there was no associated reflex tachycardia or significant rebound hypertension. In light of the pilot nature of that study, and the lack of central hemodynamic monitoring, the level of hypotension afforded by esmolol was limited to a 15% reduction of mean arterial pressure from baseline measured during stable isoflurane anesthesia. The purpose of this study was to compare central hemodynamic variables and plasma renin activity (PRA) in patients undergoing deliberate hypotension with isoflurane, sodium nitroprusside, or esmolol during surgical removal of intracranial arteriovenous malformation (AVM).

METHODS: After IRB approval and written informed consent, 22 patients were randomized as to primary agent for induced hypotension. Patients were premedicated with diazepam 10 mg p.o. approximately 90 min. before arrival to the operating room and midazolam 2-5 mg i.v. once I.V. access was established. Monitoring devices included lead II or V_5 ECG and direct radial artery blood pressure transduction. Anesthesia was induced with thiopental and vecuronium, and maintained with isoflurane 0.75% in nitrous oxide and oxygen. After induction, a pulmonary artery catheter was introduced via the antecubital fossa. Because the need for hypotension never occurred within the first 120 min. following induction, a relatively stable plane of anesthesia could be assured. Hypotension was induced with either isoflurane (up to 4%, n=6, Group 1), SNP (up to 8 mcg/kg/min, n=8, Group 2) or esmolol (up to 24 mg/min, n=7, Group 3). Hemodynamic variables recorded just prior to the administration of the hypotensive agent and at the attainment of stable hypotension include heart rate (HR), mean arterial pressure (MAP), systolic and diastolic blood pressure (SBP and DBP), central venous pressure (CVP), pulmonary artery occlusion pressure (PCWP), cardiac output (CO) and systemic vascular resistance (SVR). In addition, blood samples were drawn and immediately placed in chilled EDTA containing tubes, with the plasma separated and frozen for later PRA analysis by radioimmunoassay. In each group, the initial endpoint for deliberate hypotension was a 15 to 25% reduction of MAP. Comparisons between groups were made by analysis of variance and Fisher's Protected Least Significant Differences. Within group comparisons normalized to baseline values were made with the Student's t-Test, with the threshold for significance taken as $p<0.05$.

RESULTS: Hemodynamic variables obtained just before the induction of hypotension were compared to those obtained once the hypotensive endpoint was attained (TABLE 1). Pulmonary artery catheters could not be placed in 3 patients for technical reasons, while PRA results are available for only 15 patients (5 from each group) at this time. Hypotension could not be induced in 1 patient despite the administration of 4% isoflurane for 30 minutes. This patient was excluded from the analysis. All other patients attained their hypotensive endpoints with no adverse effect.

DISCUSSION: Although all 3 drugs were effective, the mechanism of the hypotensive action was different for the 3 agents. The hypotensive effect of esmolol resulted entirely from a reduction in CO, while the other 2 agents depressed SVR. SNP was associated with an increase in CO and HR, while these variables were unchanged with isoflurane and decreased with esmolol. Thus, of these 3 agents, esmolol seems to most favorably effect myocardial oxygen balance, with caution warranted in cases of compromised myocardial function. In addition, the decreased PRA seen with esmolol explains the lack of rebound hypertension once hypotension is terminated.

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TABLE 1: Hemodynamic Variables Before and During Deliberate Hypotension. MEAN±S.D.

		ISOFLURANE	SNP	ESMOLOL
HR	pre	84±15	89±8	79±10
	post	85±19	100±22*	65±11*[1]
MAP	pre	84±5	85±4	84±6
	post	66±6*	65±4*	68±4*
SBP	pre	106±7	110±6	107±7
	post	87±5*	89±7*	85±4*
DBP	pre	67±4	70±4	70±11
	post	53±5*	55±6*	56±5*
CO	pre	5.9±1.0	6.7±2.3	5.6±0.9
	post	5.5±1.1	7.7±2.6*	3.8±0.8*[1]
CVP	pre	6±4	7±4	8±3
	post	6±3	5±3	10±4
PCWP	pre	10±2	11±3	11±3
	post	9±3	8±4*	12±4
SVR	pre	1086±178	1031±311	1086±61
	post	891±169*	694±208*	1258±254[2]
PRA	pre	9.8±10.7	9.4±3.4	9.3±7.5
	post	21.3±24.6*	14.7±8.2	5.1±3.2*[2]

*significantly different than pre value. [1]significantly different changes with hypotension between all 3 agents. [2] changes with esmolol significantly different than other agents. Units: HR=bpm; SBP, DBP, CVP, PCWP=mmHg; SVR= dynes-cm-sec^{-5}, CO=l/min, PRA= ng/ml/hr.

Supported in part by DuPont Critical Care.

Title: THE ANTIEMETIC EFFECT OF THE EMULSION FORMULATION OF PROPOFOL IS NOT CAUSED BY THE LIPID EMULSION

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Introduction. The objective of this study was to investigate whether the 10% lipid emulsion in which propofol is now formulated is responsible, in part, for propofol's antiemetic effect. Prolonged nausea and vomiting after anesthesia may delay discharge of outpatients and lead to increased costs.. Propofol, a phenolic compound used for induction and maintenance of anesthesia, is excellent for short procedures, due to rapid recovery (1). It was previously formulated in Cremophor EL, a substance associated with pain on injection and anaphylactoid reactions. Postoperative nausea and vomiting were not specifically studied in early studies, and it is not clear if the early formulation had antiemetic effects. Propofol was reformulated (1983) in a lipid emulsion in order to eliminate the side-effects associated with Cremophor EL. Studies with this solution have shown a lower incidence of postoperative nausea and vomiting compared with other anesthetic agents (2). A prospective, randomized study was conducted in patients undergoing gynecological laparoscopies to examine the possible antiemetic properties of the lipid emulsion.

Methods. The protocol was approved by The University of Chicago Clinical Investigation Committee. Written informed consent was obtained from 29 unpremedicated ASA class I or II patients scheduled for laparoscopic surgery. Patients with history of liver disease, pancreatic disease, coagulopathy, heart or lung disease, metabolic disorder, or with previous adverse experience with general anesthesia were excluded. Patients were randomized to receive either the 10 % lipid solution in which propofol is emulsified (10% Intralipid®) or placebo (5% dextrose in lactated Ringer's solution). Prior to induction, all patients received tubocurarine 3 mg, glycopyrrolate 0.2 mg and fentanyl 1.5 μg/kg (*iv*). Four minutes later, anesthesia was induced with thiopental 4 mg/kg *iv*. Oral endotracheal intubation was performed after succinylcholine injection (1.5 mg/kg). Anesthesia was maintained with enflurane (0.5-2%) in nitrous oxide (N_2O) 66% and oxygen. Infusion of 10% Intralipid® or placebo was started at the same time as thiopental injection and continued for 20 min at the rate of 3 ml/min. (This amount of Intralipid ® is about four times the amount a 70 kg patient would receive when anesthesia is induced with propofol.) After intubation, an orogastric suction tube was placed and continuously suctioned until extubation. End-tidal CO2 was continuously measured with a capnometer to ascertain normoventilation in both groups. An additional 50μg dose of fentanyl was given immediately prior to placement of the laparoscopic trocar. Anesthesia level was adjusted by changing enflurane concentration to maintain hemodynamic variables within 30% of awake measurements. The patient, the nurse who performed recovery room assessment, and the nurse who determined the need for antiemetic/pain medication, were blinded to the infusion type. Postoperative analgesia was provided with *iv* fentanyl, 50μg at a time as needed or ibuprofen 600mg when the patient tolerated *po* medication. Severe emesis was treated with *iv* droperidol 0.6mg as needed. Emetic symptoms (nausea, retching, vomiting) as well as feeling of pain (none, mild, moderate,severe) were evaluated every 15 minutes in the post anesthesia care unit (PACU) by asking the patient how she felt and by asking the patient to complete a nausea and vomiting visual analog scale. Statistical analysis was by unpaired t-test and chi-square test with continuity correction.

Results. There were twelve patients in the Intralipid® group and 17 in the placebo group. The two groups were similar with regard to age, weight, height and type of surgery. Induction, maintenance and duration of anesthesia were similar between the groups. Also, times from discontinuation of N2O to extubation, orientation, ability to sit independently and to "home-readiness" were similar between the groups (table 1). Both groups received similar amounts of fentanyl, ibuprofen and droperidol in the PACU. Patients rated the feeling of postoperative pain similarly in both groups. There were no differences in nausea or vomiting during the recovery room stay when assessed with the visual analog scale. Similarly there were no significant differences in emesis between the groups during any time interval as assessed every fifteen minutes by the PACU nurse.

Discussion. The results from this study suggest that 10% Intralipid®, the lipid in the emulsion formulation of propofol, does not possess significant antiemetic effect. Both groups had similar intraoperative and postoperative course. There were no significant differences between the groups in any of the variables studied. It is concluded that Intralipid® is not responsible for the low incidence of emetic symptoms seen after propofol anesthesia.

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Table 1. Summary of findings (mean ±SD)

Group	Intralipid	D5LR
n	12	17
Age (yr)	29±6.3	30±5.1
Weight (kg)	70±10.8	66±10.6
Duration of anesthesia (min)	56±32.8	61±47
"Home ready" (min)	163±67	195±80
PACU Emetic symptoms (%)	83	88
PACU Visual analog scale (mm)		
Nausea	30±34	35±37
Vomiting	25±36	20±33

TITLE: **FAILURE RATE OF PULSE OXIMETRY IN CLINICAL PRACTICE**

AUTHORS: P.T. Overand, M.D., P.R. Freund, M.D., J.O. Cooper, M.B., L. Jacobson, M.B., S. Bosse, CRNA, B. Walker, CRNA, and F.W. Cheney, M.D.

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Introduction: The ASA is currently in the process of making the pulse oximeter a standard of monitoring care for all anesthetics. Because the failure rate of the pulse oximeter in routine clinical practice has not been documented, we prospectively studied the incidence of failure of the device in all anesthetics administered in University of Washington hospitals over a three-month period.

Methods: After obtaining institutional review permission, 6,532 consecutive anesthetics with pulse oximetry were evaluated for failure. Data were collected from all of our teaching hospitals including the University of Washington Medical Center (UWMC), Harborview Medical Center (HMC), Children's Hospital and Medical Center (CHMC), and the Veterans Administration Medical Center (VAMC). Standard practice at each hospital is to record the pulse oximeter reading on the anesthetic record at least every 15 minutes. If the anesthetist was unable to obtain a believable reading, the initials "NO" were recorded instead of an oxygen saturation value. Each day all anesthetic records were reviewed by one of the authors. Failure of the device was defined as the inability to obtain a pulse oximetry reading for 30 minutes or more during an individual case.

Results. There were 81 cases out of 6,532 anesthetics in which the pulse oximeter did not give a meaningful reading for 30 minutes or more. This represents an overall failure rate of 1.24% (Table). All hospitals had a similar rate of approximately 1% with the exception of VAMC, which had a rate of 4.25% (Table). The median ASA status in patients where the device failed was III, with 72% of the failures occurring in ASA-III or higher patients (Table). The mean duration of anesthesia in which a reading could not be obtained was 3 hours 47 minutes, and the average duration of failure was 1 hour 15 minutes.

Discussion. Our data indicate that pulse oximetry provides reliable clinical monitoring in the vast majority of cases, but that there is a small yet consistent incidence of prolonged failure of these devices in each patient population studied. Sicker patients undergoing longer operations are at the highest risk of failure. The higher rate at the VAMC hospital may be attributable to a higher mean age (Table) and/or a higher prevalence of peripheral vascular disease. The relative significance of these and other patient variables are currently being evaluated.

Table

	Overall	UWMC	HMC	CHMC	VAMC
Failures	81	14	13	21	33
Surgeries	6532	1825	1640	2291	776
Failure Rate	1.24%	.77%	.79%	.92%	4.25%
ASA:					
1	6	4	1	1	0
	(7%)	(29%)	(8%)	(5%)	-
2	16	2	0	2	12
	(20%)	(14%)	-	(10%)	(36%)
3	27	4	1	6	16
	(33%)	(29%)	(8%)	(29%)	(48%)
4	24	4	5	10	5
	(30%)	(29%)	(38%)	(48%)	(15%)
5	8	0	6	2	0
	(10%)	-	(46%)	(10%)	-
Median	3	3	4	4	3
Age:					
Mean	43	55	48	4	59
Std. Dev.	28	16	25	5	15
Anesthesia Time (hrs/min)					
Mean	3/47	5/47	2/3	5/27	2/32
Std. Dev.	2/57	3/35	1/25	3/15	1/39.
Failure Time (hrs/min)					
Mean	1/15	1/25	0/51	1/15	1/22
Std. Dev.	0/54	1/7	0/40	0/45	0/57

TITLE: PRELOAD RECRUITABLE STROKE WORK: INDEX OF MYOCARDIAL CONTRACTILITY IN CONSCIOUS AND ANESTHETIZED DOGS

AUTHORS: PS Pagel, MD, JP Kampine, MD, PhD, WT Schmeling, MD, PhD and DC Warltier, MD, PhD
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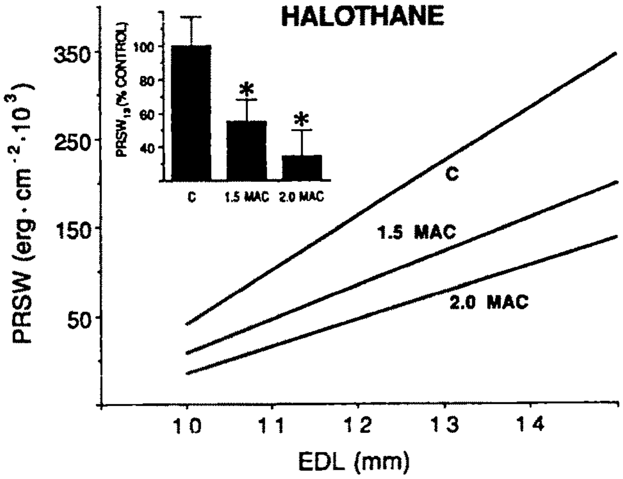
Introduction: Reliable *in vivo* quantification of myocardial contractility has been elusive. Previously available estimates of function have inherent problems such as non-linearity, dependence on changes in afterload, and difficulty with numerical assessment. It has been demonstrated that the relationship between regional stroke work and end diastolic length (EDL), termed preload recruitable stroke work (PRSW), was a linear, afterload insensitive measure of intrinsic inotropic state in both normal[1] and ischemic[2] myocardium. The purpose of this investigation was to compare the effects of isoflurane (I) and halothane (H) on myocardial contractility as measured by PRSW in chronically instrumented dogs. Pharmacological blockade of the autonomic nervous system was utilized to prevent reflex changes in systemic hemodynamics during alterations in left ventricular preload in the conscious and anesthetized state.

Methods: After Institutional Animal Care Committee Approval, mongrel dogs (n=8) were anesthetized and instrumented under sterile conditions for measurement of aortic blood pressure, left ventricular pressure, +dP/dt, and cardiac output. Ultrasonic segment length transducers were implanted in the left ventricular subendocardium to assess regional contractility. A hydraulic vascular occluder was placed around the inferior vena cava (IVC) to sequentially alter preload. Dogs were allowed to recover from surgery 7-10 days prior to experimentation. After recording baseline hemodynamics and segment length, dogs were autonomically blocked with propranolol (2 mg/kg), atropine methylnitrate (3 mg/kg) and hexamethonium (20 mg/kg). Once adequacy of pharmacologic blockade and confirmation of a hemodynamic steady state had been achieved, pressure and segment length data for loop generation were recorded in the conscious (C) state. The IVC was then constricted to reduce left ventricular systolic pressure in 10 mmHg decrements. End expiratory pressure-length loops of 6-8 cardiac cycles were obtained at 3 decremental levels of left ventricular systolic pressure. Following inhalation induction, anesthesia was maintained at 1.5 MAC of H or I. After one hour of equilibration, pressure-length loops were obtained in the manner described above. H or I was then increased to 2 MAC and measurements were repeated after similar equilibration. Arterial blood gases were maintained at conscious levels throughout the experiment and blood anesthetic concentrations were verified by gas chromatography. Pressure and segment length data were recorded on analog tape and transmitted to a digital storage oscilloscope for loop generation. Changes between control (conscious) and anesthetic concentrations were compared by ANOVA with repeated measures followed by Fisher's LSD test ($^*p<0.05$).

Results: When regional PRSWA was plotted as a function of EDL, linear relationships consistently resulted (mean $r^2 \geq 0.94$) in all groups. Different concentrations of H progressively and significantly decreased the slope (61.0±11.1 for control to 30.4±6.9 $erg \cdot cm^{-3} \cdot 10^3$ for 2 MAC) and increased the x=intercept (EDL of 9.2±0.3 to 10.9±0.7 mm) consistent with a reduction in contractility (Figure). Concomitant decreases in +dP/dt were observed. Decreases in slope 88.2±14.8 to 57.5±8.5 $erg \cdot cm^{-3} \cdot 10^3$ at 2 MAC) and increases in x-intercept (EDL of 10.4±0.8 to 12.1±1.1 mm) were also observed for I. PRSW at a constant EDL of 13 mm as an index of contractility demonstrated similar results. Equipotent concentrations of H and I resulted in significantly decreased regional work at constant preload (Figure insert).

Discussion: The results of this investigation indicate that the relationship between PRSW and EDL provides a reliably linear index of myocardial contractility in the conscious and anesthetized state. The volatile anesthetics H and I both predictably decreased PRSW at varying levels of preload consistent with the negative inotropic effects of these agents. The results also suggest that comparisons between intrinsic inotropic states at equipotent doses of different inhalational agents can be made.



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Title: **UTERINE CIRCULATORY CHANGES OF HUMAN PREGNANCY**

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Introduction: Initial studies with a newly-developed Doppler[1] were undertaken to obtain noninvasive information about uterine circulatory changes during human pregnancy. The new Doppler produces and displays an instantaneous mean flow velocity (MFV) waveform during the entire cardiac cycle. Because of its unique characteristics, this Doppler can yield quantitative estimation of uterine blood flow.

Methods:

After approval by the human research committee, ten volunteer women who gave written informed consent were studied in thirty sessions during pregnancy and/or postpartum using both the new Doppler instrument and a commercially available ultrasound, the Acuson 128. The new instrument was compared with the commercial Doppler, and data from both instruments used to verify accuracy of flow velocities. Pregnant patients were studied with a hip wedge in place to avoid aorto-caval compression. Arteries studied included the common iliac (CI), external iliac (EI), internal iliac (II), and uterine arteries (UA). The Acuson allowed us to locate vessel anatomy, measure vessel diameters, measure actual angles of insonation, and calculate the mean peak systolic velocity adjusted to a zero angle of insonation.

The new Doppler has a unique signal generating and processing capability, which permits display of the instantaneous mean flow velocity during the entire cardiac cycle in the blood vessels studied. This information can be combined with the Acuson diameter measurements to estimate volumetric blood flow by the following formula: Flow=(MFV)(pi)(r^2)

Results:

For some of the study sessions, blood vessels were imaged using the echo mode of the Acuson, and the actual angle of insonation for the new Doppler was measured. An average angle of insonation could be found for each blood vessel studied. (CI=27.8°±7.4, EI=36.0°±7.2, II=58.8°±4.9, UA=20.8°±14.4) The MFV obtained with the Doppler were then corrected from programmatic assumed angles to yield the values listed in Table II. Results in the following tables are displayed as mean values ± SEM. N for each cell in the tables varies from 1-5.

TABLE I: DIAM(CM)

WKS PG	20	30	36	PP
CI	.68±.26	.67±.04	.69±.05	.79±.06
EI	.55±.06	.54±.04	.57±.01	.50±.09
II	.47±.04	.45±.03	.52±.03	.38±.08
UA	.29±.03	.29±.02	.30	.17±.02

TABLE II: MFV(CM/SEC)

WKS PG	20	30	36	PP
CI	18.6±2.1	14.4±2.1	18.7±3.6	16.2±2.8
EI	14.9±1.7	12.8±1.4	18.5±3.8	17.7±2.0
II	40.9±3.9	41.1±6.7	47.6±10	13.9±2.5
UA	39.9±4.8	39.3±3.6	70.5±14	11.7±3.0

TABLE III: FLOW (ML/MIN)

WKS PG	20	30	36	PP
CI	514±319	299±67	460±126	426±97
EI	222±47	171±22	193±78	275±27
II	274±59	291±65	380±130	132±41
UA	129±21	189±23	217	27±11

As the Tables show, CI, EI, II diameters do not change much during pregnancy. UA diameter doubles during pregnancy. Further, this doubling occurs early in the pregnancy since it was already present when determined in three studies before the 24th week of gestation. CI, EI mean flow velocities (MFVs) do not change much during pregnancy. II MFV increases during pregnancy. UA flow increases most dramatically achieving more than a sixfold increase before the third trimester. Velocity increases then account for all of the increasing UA flow of late pregnancy.

Discussion:

Information was gained about the usual angles of insonation for the major arteries supplying the uterus during the course of pregnancy. Some vessels, e.g. II, are more difficult to insonate and the average angle of II insonation was nearly 60°. When angles are > 30°, large errors in flow velocity can be introduced if the actual angles of insonation are not known.

This study has added to our knowledge of human vascular anatomy and flow relationships during pregnancy. More refined velocity data and quantitative estimation of uterine blood flow is made possible by the use of a new Doppler instrument. Quantitative flow information may prove more sensitive in detecting abnormal pregnancies than currently used relative indices of systolic:diastolic flow velocities[2]. The newly introduced Doppler should prove to be very useful in other vascular beds which are also difficult to study. The more accurate MFV waveforms may also assist in the monitoring of therapy or evaluation of effects of anesthetics on the characteristics of organ blood flow.

References:

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Title: VENTILATORY RESPONSE TO CARBON DIOXIDE BEFORE AND AFTER INHALATION ANESTHESIA IN INFANTS

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Introduction: Halothane causes a dose-dependent depression of ventilatory response to CO_2, although at very low concentrations there is no effect (1). The ventilatory response to CO_2 after halothane/N_2O anesthesia for infants has not been determined. This may in part be due to the difficulty in obtaining measurements of ventilation with infants. The purpose of this study is to measure the ventilatory response to CO_2 for infants before and after halothane/N_2O anesthesia using a maskless CO_2-response test (2).

Methods: Ventilatory response to CO_2 was measured before and after halothane/N_2O anesthesia for 6 infants. This project was approved by the institutional human research review committee, and written consent was obtained. (All numbers are mean ± SD).

Subjects: Infants were ASA class I, 13.6 ± 3.5 wks of age and 4.6 ± 1.4 kg. Post-conceptual age was 49.5 ± 4.4 wks. None had a history of apnea. Five underwent repair of inguinal hernias and 1 had excision of a lip hemangioma. All received inhalation anesthesia with halothane and N_2O; 3 also received local anesthesia and 1 had codeine. The duration of anesthesia was 1.4 ± 0.4 hrs.

CO_2-response Test: For the maskless CO_2-response test, a ventilatory ratio is calculated from skin-surface (transcutaneous) PCO_2 measurements. This ratio indicates the proportional increase in steady-state ventilation that occurs when a subject breathes added CO_2. The calculation of ventilatory ratio is as follows:

$$VR = \frac{bP_SCO_2}{(cP_SCO_2 - cP_ICO_2)}$$

VR = ventilatory ratio
bP_SCO_2 = baseline skin-surface PCO_2 (mmHg) with no added CO_2
cP_SCO_2 = skin-surface PCO_2 (mm Hg) with added CO_2
cP_ICO_2 = inspired PCO_2 (mm Hg) with added CO_2

Ventilatory ratios were calculated for two levels of added CO_2 - 2% and 4%. The tests were conducted with the infants in quiet sleep. Inspired gases included 30% O_2 and were delivered through a respiratory hood. The skin electrode (Transend™, Sensormedics, Inc.) was applied for ≥ 20 min. before bP_SCO_2 was recorded. Then 2% CO_2 was added to the inspired gas, and after equilibration ≥ 10 min. the test reading was made. The same procedure was repeated with 4% CO_2.

The CO_2-response test was performed before anesthesia, and again after discharge from the recovery room (1.3 ± 0.3 hrs after anesthesia). VRs before and after anesthesia were compared by paired t test. Statistical significance is $p<0.05$.

Results:

	Before Anesthesia	*After Anesthesia*	*p*
VR 2% CO_2	1.44 ± 0.08	1.46 ± 0.09	0.28
VR 4% CO_2	2.58 ± 0.35	3.00 ± 0.66	0.06
bP_SCO_2 (mm Hg)	43.5 ± 1.3	38.6 ± 3.4	0.01

There is no significant change in VR after halothane/N_2O anesthesia in these infants. It is of interest to note, however, that baseline P_SCO_2 is significantly lower after anesthesia.

Discussion: These results indicate that ventilatory response to CO_2 is not depressed after halothane/N_2O anesthesia in infants. This is consistent with findings that ventilatory response to CO_2 matures early in life (3), and halothane in low dose has no effect on the response (1).

For 4 of the 6 infants VR with 4% CO_2 increased after anesthesia [Fig. 1]. This and the significant decrease in baseline P_SCO_2 after anesthesia may reflect development of a metabolic acidosis during the anesthesia/surgical period. Further studies are necessary to verify this.

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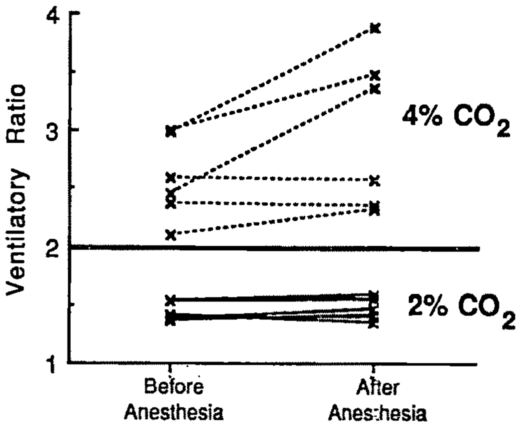

Figure 1. Ventilatory ratios for 6 infants.

Title : WHICH VOLATILE ANESTHETIC FOR OUTPATIENT ANESTHESIA? QUALITY AND SPEED OF RECOVERY

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Introduction. Because of its low blood gas solubility, isoflurane is most often chosen as the volatile anesthetic for outpatient anesthesia. We compared the quality and speed of recovery after isoflurane and enflurane based anesthesia in a double blind fashion.

Methods. Our Institutional Review Board approved the study and each patient gave written informed consent. Forty-five adult female patients, physical status ASA I or II, scheduled for an outpatient laparoscopic procedure were studied. Patients, stratified into smokers and nonsmokers received equal MAC concentrations of either isoflurane or enflurane with nitrous oxide based anesthesia. No narcotic or anti-emetic were used. Quality (coughing, secretions, laryngospasm, etc.) as well as speed (orientation, ambulation, discharge times, psychomotor function tests, etc.) were noted by a blinded observer. Side effects (e.g., nausea, vomiting, shivering, etc.) were also observed.

Results. The groups were comparable demographically. There were no differences between the two anesthetic groups either in respect to quality or speed of recovery or in the incidence of side effects. Coughing and secretions were more common among the smokers ($p<0.05$). Seventy-six percent of all patients complained of severe pain on arrival to the recovery room and needed intravenous fentanyl immediately. Fifty-eight percent of all patients had nausea and or vomiting, 29% required an anti emetic therapy.

Conclusion. We conclude that there is no difference in either quality or in speed of recovery after isoflurane or enflurane anesthesia. There is no advantage of avoiding intraoperative narcotic and prophylactic anti-emetic in female outpatients undergoing laparoscopic procedure.

Table 1

Variables for quality and speed of recovery

Variables	Isoflurane (N=23)	Enflurane (N=22)
Smoker/ non smoker	12/11	11/11
Coughing in OR (any)	11	11
Laryngospasm in OR (any)	4	3
Shivering in PACU (>2 mins)	15	8
Orientation (mins), mean ± S.D.	12.5±5.4	11.6±3.9
Discharge time (mins), mean ± S.D.	162.9±34.9	158.2±38.4
I.V narcotic in PACU	18	16
Nausea and/or vomiting (PACU)	13	13
P del test, lines compl	22.2±5.6	23.8±5.8
Trieger test, dots missed	3.6±4.5	4.2±4.7
Can smell anesthetic (mins)	387.8±419	427.7±305
Muscle ache (24 hours)	3	4
Light headed at home	5	2
Sore throat (any)	15	16
> 24 hours to normal activity	5	2

No significant difference in any of the variables between two groups.(ANOVA and chi square analysis)

Title: REGIONAL BLOOD FLOW DISTRIBUTION DURING SEVERE INSPIRATORY FLOW RESISTIVE LOADING IN AWAKE SHEEP

Authors: L. M. Pang, M.D., A. R. Bazzy, M.D., S. R. Akabas, Ph.D., G. G. Haddad, M.D.
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Introduction: The arterial supply to the diaphragm originates from several sources and anastomoses freely with each other. This suggests that blood flow and energy supply to the diaphragm should be adequate when the respiratory work load is increased. However, diaphragmatic failure has been reported in situations during which the metabolic demands of the diaphragm have been increased by either whole body exercise (1) or respiratory loading (2). The cause of this failure, eg, the limited supply of blood-borne energy substrates or the availability of oxygen to the diaphragm, is not clear. The purpose of the study was to determine the regional distribution of blood flow to the muscles of respiration and major organs at rest and during a severe inspiratory flow resistive (IFR) load in unanesthetized chronically catheterized sheep in order to ascertain the availability of oxygen and blood supply.

Methods: The project was approved by the committees on animal investigation of the two institutions.

Approximately two weeks prior to the experimental day, a left atrial catheter was inserted via a left thorocotomy under general anesthesia. One week later, arterial and external jugular catheters were inserted and a tracheostomy was performed under general anesthesia. On the day of the experiment, a Swan-Ganz catheter was floated into the pulmonary artery and two thin-walled latex balloon catheters were inserted via the nares into the rumen and the middle third of the esophagus. The animals were allowed to stand in their slings for at least one and one-half hours before beginning the experiment.

Continuous recordings of the systemic arterial, pulmonary arterial, pulmonary capillary wedge, esophageal, gastric and transdiaphragmatic (Pdi) pressures and airflow were obtained. Thermodilution cardiac outputs were performed in triplicate. The tracheostomy tube was connected to a Hans-Rudolph valve. Inspiratory flow resistive loads consisted of narrow-bore endotracheal tube adaptors which were connected to the inspiratory limb of the Hans-Rudolph valve. The expiratory limb of the valve was opened to atmosphere. Regional blood flow was determined by the radioactive microsphere technique during quiet breathing, then after an average of 9, 40 and 60 minutes on a severe IFR load. At the end of the experiment tissues were obtained after euthanasia solution was administered. Tissues were counted in a 3-channel gamma counter for 10 minutes.

Results: The results of some of the data are summarized on Table 1. When the two muscle regions of the diaphragm were analyzed independently, both regions had a significant increase in blood flow at 40 and 60 mins over baseline. There were no differences in blood flow between the two regions at any time. Blood flow to all the muscles of respiration increased significantly over baseline. Only the major organs which showed a significant change in blood flow are shown on Table 1.

Table 1. The mean (SEM) physiologic and blood flow (ml/min/100gm) data are shown. (* p 0.05 from baseline; ** p 0.05 from 40 mins)

	Baseline	9 mins	40 mins	60 mins
Pdi (cm H_2O)	9	72*	80*	64* **
	(1.7)	(19.7)	(10.5)	(9.3)
$PaCO_2$(mmHg)	35	51*	59*	77* **
	(4.4)	(9.1)	(13.6)	(12.2)
Diaphragm	28	146*	266*	201*
	(5.0)	(53.9)	(49.7)	(26.8)
Expir Muscles	8	17	32*	28*
	(3.4)	(5.6)	(11.2)	(5.5)
Brain	78	194*	225*	239*
	(4.3)	(42.2)	(30.4)	(25.5)
Heart	96	146	222*	185
	(8.6)	(15.3)	(42.2)	(19.6)
Pancreas	391	285	311	125*
	(62.1)	(62.5)	(95.1)	(39.1)

Discussion: This study shows that blood flow to the expiratory as well as inspiratory muscles of respiration increased during severe IFR loads and that there is no significant decrease in blood flow to the diaphragm despite evidence that the diaphragm is beginning to fail.

In separate studies under similar conditions (3) we have shown that blood oxygen tension in the phrenic vein, one of the major channels draining the diaphragm, is still rising at the time the diaphragm begins to fail and changes in lactate and pyruvate concentrations were small and inconsistent.

From these two studies, we reason that O_2 delivery to the diaphragm is greatly increased and speculate that the large increase in blood flow to the diaphragm may be necessary to deliver sufficient amounts of energy substrates to the diaphragm but that oxygen requirements of the diaphragm could probably be met with smaller increases in blood flow.

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3. AR Bazzy, LM Pang, SR Akabas, GG Haddad: O_2 metabolism of the sheep diaphragm during flow resistive loaded breathing. J Appl Physiol 66:2305-2311, 1989.

Title:

DIFFERENCES IN SUSCEPTIBILITY TO DIAPHRAGMATIC FATIGUE AND RECOVERY FROM NEWBORN TO ADULT RAT. EFFECT OF AMINOPHYLLINE.

Authors: Richard I. Park, B.A., Silvio Glusman, M.D., Ph.D.
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Introduction:

Diaphragmatic fatigue plays a major role in respiratory failure. It has been proposed that neonates are more prone than adults to diaphragmatic fatigue. A recent study showed that methylxanthines, in particular aminophylline, accelerates recovery from diaphragmatic fatigue in adult rats. We studied fatigue and recovery from fatigue in isolated rat diaphragms at different stages of development, from newborn to adults, and compared the effect of aminophylline at each stage.

Methods:

After approval by the Animal Care Committee, Sprague-Dawley rats aged 3 days to adults were anesthetized with ether, and a strip of the diaphragm was removed and continuously perfused with a modified Ringer's solution aerated with 95% O_2/5% CO_2. The costal margin of the diaphragm was fixed to the bottom of the perfusion chamber and the central tendon was connected to a force transducer. The diaphragm was supramaximally stimulated (3x threshold) with bipolar platinum wires. Trains (260 msec duration, 20 Hz) were delivered at 0.1Hz and contractile tension was recorded with a pen recorder. To induce fatigue, the frequency of stimulation was increased to 1.0 Hz for 3 minutes. Recovery from fatigue was studied by examining the recovery of tension upon return to 0.1 Hz. All the experiments were performed in the presence of *d*-tubocurarine, 6 ug/cc.

Results:

The degree of diaphragmatic fatigue and recovery from fatigue is closely related to age. In all age groups, high frequency stimulation induced a decrease in the contractile force that the diaphragm generated. Stimulation of the diaphragm for 3 minutes at 1 Hz reduced the contractile force in the 4 to 20 day old rats by 15-20%, whereas in the 50 day old and adult rat the reduction was 31% and 47% respectively (Fig1). Recovery from fatigue was faster in the diaphragm of newborn rats and decreased with age. The t1/2 of recovery was 16 sec. in rats 4-7 days old; 180 sec. in rats 20 days old; 620 sec. in rats 40-50 days old; and 1768 sec. in adults. Aminophylline increased the contractile force in the diaphragm in all age groups in a dose-related manner. Aminophylline did not decrease the degree of tension in the diaphragm of fatigue in all developmental stages. In adult diaphragms, aminophylline greatly accelerated the rate of recovery from fatigue (t1/2=450 sec., Fig3). It was ineffective in changing the time course of recovery from fatigue in young diaphragms (Fig 2).

Discussion:

This study shows that there are developmental differences in the contractile properties of the diaphragm from neonate to adult rat regarding propensity to fatigue and recovery from fatigue. Diaphragms of neonate and young rats are more resistant to fatigue than are those of adult rats. Recovery from diaphragmatic fatigue is much faster in the newborn and young vs. the adult rat. The diaphragm is a mixed muscle composed of various proportions of slow (fatigue-resistant) and fast (fatigue-resistant and fatigue-susceptible) fibers. There is evidence that the proportion of the different types of muscle fibers in the diaphragm may change from newborn to adult. Our results may be explained on the basis of varying proportion of different types of muscle fibers during development. It is possible that the greater proportion of fast(fatigue resistant) to fast(fatigue susceptible) fibers that may exist in the newborn diaphragms changes during rat development.

Aminophylline increases contractile force in the rat diaphragm in all ages; however, the degree of fatigue is not affected. Although aminophylline clearly accelerates the recovery from fatigue in the adult diaphragms (Fig. 3), it is ineffective in speeding the recovery in young diaphragms (Fig.2). This suggests that there may exist different mechanisms in the recovery from fatigue between the newborn and adult rat.

Reference:

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Fig1. Different age rats

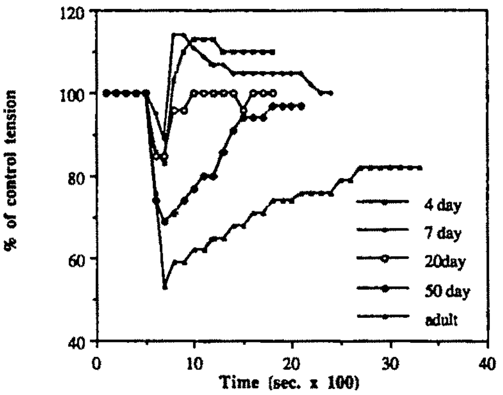


Fig2. 4 day old rat

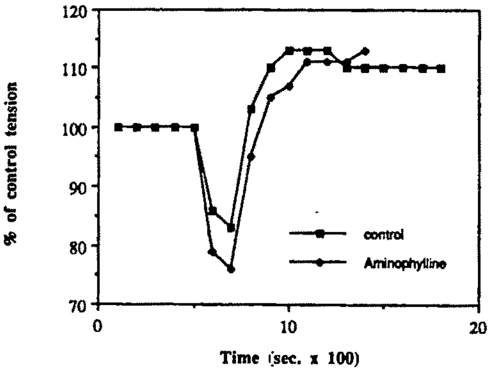
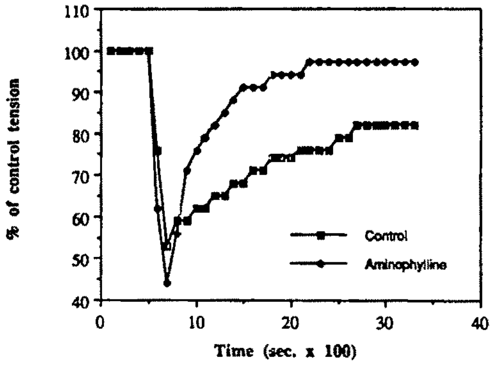


Fig3. Adult rat



TITLE: EPIDURAL PCA: EFFECT OF A CONTINUOUS (BASAL) INFUSION ON THE POSTOPERATIVE OPIOID REQUIREMENT

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Introduction: Epidural opiate therapy can provide effective analgesia in the postoperative period. Preliminary studies suggested that continuous epidural opioid and/or local anesthetic infusions produce more effective analgesia with less medication than the traditional intermittent injection techniques (1,2). Patient-controlled analgesia (PCA) delivery systems can provide for optimal titration of analgesic medication and are useful in quantitating the opioid analgesic requirement. Therefore, we designed a study comparing the analgesic effectiveness and recovery profile when epidural opioids were administered using a PCA device programmed to deliver either incremental bolus doses or a "basal" infusion supplemented by bolus doses on demand for management of pain after cesarean delivery.

Methods: Thirty-five consenting ASA I-II women scheduled to undergo elective cesarean delivery were randomly assigned to one of two treatment groups according to an IRB-approved protocol. All patients received lumbar epidural anesthesia with bupivicaine 0.5%, 15-25 ml, for the operative procedure. On arrival in the recovery room, patients in both groups received a loading dose of hydromorphone (HM) (Dilaudid^{R}), 0.9 mg (6 ml), via a Bard Ambulatory PCA™ device. In Group I (basal infusion plus PCA), the device was programmed to deliver a continuous HM infusion, 0.045 mg (0.3 ml), which could be supplemented with HM, 0.15 mg (1 ml), every 30 min, PRN. In Group II (PCA alone), the device was programmed to deliver incremental HM, 0.15 mg (1 ml) bolus doses every 30 min (PRN). Postoperative assessments included HM dosage requirements as well as pain (0 = no pain to 100 = severe pain) and sedation (0 = wide awake to 100 = almost asleep) analog scales at 8 hr intervals. Records of the number of PCA demands and doses delivered were also analyzed. In addition, recovery times to ambulation, return of bowel function, resumption of oral intake and normal diet, and hospital discharge were determined. Data were analyzed using ANOVA and Chi-square, p<0.05 was considered significant.

Results: The two treatment groups were similar with respect to demographic data (Table 1). Pain and sedation analog scores were virtually identical at all study intervals. Surprisingly, the number of supplemental bolus doses demanded (and delivered) did not differ significantly between the two groups (Table 2). Hence, the basal infusion plus bolus group (I) received significantly more analgesic medication than the group (II) receiving intermittent bolus doses alone. Although the infusion group received more medication than the bolus alone group, the incidence of side effects (Table 3) and recovery times (Table 4) were similar.

Discussion: Our results indicate that epidural PCA can provide effective postoperative analgesia with small doses of opioid medication. Although a preliminary study with the epidural infusion-PCA technique was highly effective in treating postoperative pain (3), we were unable to demonstrate any significant benefit of a "basal" infusion with epidural PCA compared to the traditional incremental dosing method. In fact, the higher opioid requirement and similar incidence of side effects in the infusion plus PCA (vs PCA alone) group suggests that tolerance may develop more rapidly to the effects of epidural opioid infusions than with an incremental bolus administration technique.

References:
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Table 1: Demographic data for Group I (infusion + PCA) and Group II (PCA alone) (Means ± S.D.)

	Group I	Group II
Age (years)	29.2 ± 5.8	26.5 ± 6.6
Height (cm)	65.1 ± 2.6	63.7 ± 3.0
Weight (kg)	85.2 ± 16.0	80.9 ± 20.9
Surgery (min)	74.2 ± 29.2	71.6 ± 26.9

Table 2: Number of supplemental bolus doses and demands and hydromorphone requirement (mg) at 8h intervals during the postoperative period for Groups I and II

Time	Ratio of bolus:demands		Hydromorphone requirement (mg)	
Intervals (h)	I	II	I	II
0-8	4:10	3:6	1.83 ± 0.48	1.42 ± 0.51*
8-16	4:8	3:4	0.98 ± 0.62	0.51 ± 0.32*
16-24	4:7	4:5	0.96 ± 0.60	0.58 ± 0.36*
24-32	4:6	3:4	0.84 ± 0.67	0.49 ± 0.34
32-40	3:5	3:4	0.77 ± 0.62	0.48 ± 0.34

* Significantly different from Group I, p<0.05

Table 3: Recovery data for the two treatment groups (hr)

	Group I	Group II
Ambulation	21.6 ± 5.5	26.1 ± 6.1
Bowel sounds	28.8 ± 13.0	25.6 ± 10.8
Regular diet	66.6 ± 35.2	61.0 ± 23.1
Discontinue PCA	40.8 ± 16.8	37.4 ± 12.7
Oral analgesic (p PCA)	7.1 ± 8.3	11.9 ± 11.7
Hospital discharge	106.9 ± 26.9	125.3 ± 70.7

Table 4: Incidences of side effects during PCA therapy (%). Patients requiring treatment are noted in parenthesis (%).

	Group I	Group II
Nausea	22(17)	25(19)
Vomiting	22(17)	19(13)
Pruritis	44(22)	62(19)
Constipation	5(5)	6(0)
Urinary retention	0(0)	6(0)

TITLE: USE OF EPIDURAL PCA FOR POST-OPERATIVE PAIN MANAGEMENT: EFFECT OF LOCAL ANESTHETIC ON THE OPIOID REQUIREMENT

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Introduction: Epidural opioid therapy has become increasingly popular in the treatment of pain after elective cesarean delivery. Recent studies would suggest that the use of opioid-local anesthetic combinations may offer advantages over opioids alone in the management of acute postoperative pain (1,2). We designed a clinical study to evaluate the analgesic effectiveness and recovery characteristics of an epidural opioid infusion when compared to a combination opioid-local anesthetic infusion after cesarean delivery. In order to optimize the titration of the analgesic medication, patients were allowed to self-administer supplemental doses of the opioid or opioid-local anesthetic combination using a patient-controlled analgesia (PCA) device.

Methods: Forty healthy consenting young women were randomly assigned to one of two treatment groups according to an IRB-approved protocol. All patients received a lumbar epidural with bupivacaine 0.5%, 15-25 ml, for the operative procedure. Prior to discharge from the recovery room, the patient's epidural catheter was connected to a Bard Ambulatory PCA™ device. After receiving a standardized loading dose, patients were administered a basal infusion of either hydromorphone 0.15 mg·ml^{-1}, alone (Group I), or a hydromorphone 0.02 mg·ml^{-1}, bupivacaine 0.08%, epinephrine 5 µg·ml^{-1} combination (Group II), both of which could be supplemented with 1-5 ml bolus doses "on demand". Postoperative assessments were performed by a "blinded" observer at 8 h intervals and included analgesic drug requirement, pain (0=no pain to 100=severe pain) and sedation analog scales, side effects and recovery times (to ambulation, return of bowel function, resumption of oral intake and normal diet, and hospital discharge). Data were analyzed using ANOVA and Chi-square, with $p<0.05$ considered significant.

Results: The two groups were comparable with respect to demographic data (Table 1). Visual analog scores for pain and sedation were virtually identical for the two treatment groups. Although Group II received an average of 22-36 mg of bupivacaine per 8 h interval, the hydromorphone requirements did not differ between the two groups (Table 2). Side effects were similar (Table 3), however, leg hypesthesia and weakness was more common in the local anesthetic group (II). Recovery times were also similar for the patients receiving epidural opioids and the opioid-local anesthetic combination (Table 4).

Discussion: Epidural analgesia provides effective pain relief in the early postoperative period. In this study, we were unable to demonstrate any beneficial effect with respect to analgesic efficacy, side effects or recovery parameters when an epidural opioid-local anesthetic combination was compared to use of an opioid alone. In conclusion, the epidural hydromorphone (0.1 mg·h^{-1})-bupivacaine (4 mg·h^{-1})-epinephrine (25 µg·h^{-1}) combination was not significantly more effective than epidural hydromorphone alone for management of pain after elective cesarean delivery.

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Table 1: Demographic data for the hydromorphone (I) and hydromorphone-bupivacaine-epinephrine combination (II) treatment groups (mean values ± S.D.)

	Group I	Group II
Age (yr)	29.2 ± 5.8	27.9 ± 7.7
Height (cm)	65.1 ± 2.6	64.8 ± 2.5
Weight (kg)	85.2 ± 29.2	84.5 ± 22.3
Surgery (min)	74.2 + 29.2	61.1 + 19.7

Table 2: Hydromorphone requirement (mg) at 8h intervals during the early postoperative period

Time interval (hr)	Group I	Group II
0-8	0.96 ± 0.54	0.78 ± 0.20
8-16	0.98 ± 0.63	0.77 ± 0.35
16-24	0.94 ± 0.62	0.77 ± 0.34
24-32	0.84 ± 0.67	0.69 ± 0.38
32-40	0.77 + 0.62	0.56 + 0.37

Table 3: Incidence of common side effects during epidural PCA therapy (% requiring therapy in parenthesis)

	Group I	Group II
Nausea	22(17)	31(19)
Vomiting	22(17)	13(13)
Pruritis	44(22)	62(31)
Constipation	5(5)	6(6)
Urinary retention	0(0)	6(6)
Leg hypesthesia	0(0)	54(54)*
Leg weakness	5(0)	15(5)

*Significantly different from Group I, $p<0.05$

Table 4: Recovery times (hrs) from the end of surgery until specific endpoints were achieved (mean values ± S.D.)

	Group I	Group II
Ambulation	21.5 ± 5.5	24.1 ± 5.5
Bowel sounds	28.8 ± 13.0	24.3 ± 15.0
Regular diet	66.6 ± 35.2	51.6 ± 24.2
Discontinue PCA	40.8 ± 16.8	33.4 ± 16.8
Oral analgesic (p PCA)	7.1 ± 8.3	12.2 ± 20.6
Hospital discharge	106.9 + 26.9	102.6 +17.5

TITLE: INITIAL CLINICAL EVALUATION OF PENTAMORPHONE: A NEW OPIOID ANALGESIC

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Introduction: Pentamorphone (A-4492) is a new potent, rapid and short-acting morphinan derivative with analgesic properties. In healthy male volunteers, Glass et al. reported that pentamorphone, 0.12-0.24 $\mu g \cdot kg^{-1}$ iv, decreased experimental pain without producing intolerable side effects (1). We designed a preliminary clinical dose-ranging study to evaluate the safety and efficacy of pentamorphone when administered for the treatment of acute postoperative pain.

Methods: Twenty-eight consenting ASA I-II adult patients, 18-59 yrs, scheduled to undergo lower abdominal operations were randomly assigned to one of four treatment groups according to a double-blind, IRB-approved protocol. All patients received a standard anesthetic technique consisting of fentanyl 2.5 $\mu g \cdot kg^{-1}$, thiopental 4 $mg \cdot kg^{-1}$ and succinylcholine 1 $mg \cdot kg^{-1}$, iv, for induction and isoflurane 0.5-1.5% and nitrous oxide 60% in oxygen for maintenance of anesthesia. When the patient complained of moderate-to-severe pain in the recovery room (medication time), they were asked to indicate the degree of pain (0=none to 100 = excruciating) on an analog scale. The study medication (pentamorphone 0.08, 0.16 or 0.24 $\mu g \cdot kg^{-1}$) or placebo (saline), 3 ml iv, was then administered over 60-90 sec. Measurements of pain, sedation (1=none to 4=marked), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR) and oxygen saturation were repeated at intervals of 5, 10, 15, 30 and 60 min. If the pain was not relieved by the study medication within 10 min, the patient was administered morphine, 1-2 mg iv increments, as needed to control the pain. The time to morphine "rescue" and the total amount of morphine required to control acute pain in the recovery room were recorded. Subsequently, patients were allowed to use a patient-controlled analgesia (PCA) device to control their pain until they were able to tolerate oral analgesics. The four groups were compared using ANOVA and Chi-square analysis, $p<0.05$ was considered significant.

Results: The four groups were comparable with respect to demographic data, intraoperative opioid administration, anesthesia time and time to medication in the recovery room (Table 1). Although the highest dose of pentamorphone, 0.24 $\mu g \cdot kg^{-1}$, tended to prolong the "rescue time" and decrease the amount of morphine required to control pain in the recovery room (Table 2), there were no significant differences in pain scores after drug administration. In addition, pentamorphone, 0.08-0.24 $\mu g \cdot kg^{-1}$, produced no acute cardiorespiratory changes (Table 3). The PCA morphine usage during the first 24 h was also similar in all four groups. Finally, no adverse reactions or side effects were reported.

Discussion: This preliminary dose ranging study suggests that pentamorphone doses larger than 0.24 $\mu g \cdot kg^{-1}$ will be required to produce analgesia after major (intra-abdominal) operations. Although pentamorphone 0.16-0.24 $\mu g \cdot kg^{-1}$ produced a transient opioid-sparing effect without any clinically significant side effects, further studies involving larger doses are needed to define the risk:benefit ratio for pentamorphone in the postoperative setting.

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Table 1: Demographic data (mean ± S.D.)

Dose ($\mu g \cdot kg^{-1}$)	0	0.08	0.16	0.24
Number (n)	7	8	7	6
Age (yrs)	47±11	50±20	40±11	43±10
Weight (kg)	69±12	77±19	73±14	63±16
Height (cm)	163±07	165±10	170±07	159±17
Fentanyl (µg)	161±45	175±75	154±58	167±52
Anesthesia time (min)	205±71	177±52	140±45	176±64
Medication time (min)	31±16	35±14	22±16	32±06

Table 2: Efficacy (analgesia) data

Dose ($\mu g \cdot kg^{-1}$)	0	0.08	0.16	0.24
Pain scores (mm)				
@ 0 min	76±19	72±20	66±31	72±39
@ 5 min	77±21	67±32	65±22	57±18
@ 10 min	74±17	67±36	57±21	63±22
Time to rescue (min)	25±13	27±17	37±28	51±45
Morphine required (mg)	7±5	5±4	5±4	3±2

Table 3: Cardiorespiratory changes

Dose ($\mu g \cdot kg^{-1}$)	0	0.08	0.16	0.24
Mean arterial pressure				
@ 0 min	95±19	94±17	96±22	99±12
@ 5 min	90±16	91±16	96±23	92±11
@ 10 min	89±19	91±16	96±25	92±13
Heart rate				
@ 0 min	83±10	71±10	70±17	86±13
@ 5 min	77±42	66±08	65±12	76±12
@ 10 min	75±10	63±05	67±14	84±15
Respiratory rate				
@ 0 min	19±04	18±03	17±04	17±03
@ 5 min	20±03	18±02	17±02	17±02
@ 10 min	21±05	18±03	17±03	19±03

TITLE: COMPARATIVE EFFECTS OF MAGNESIUM AND BRETYLIUM ON BUPIVACAINE CARDIOVASCULAR TOXICITY

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Introduction: Magnesium (Mg) and bretylium have both been studied regarding their efficacy in preventing dysrhythmias secondary to bupivacaine toxicity.(1,2) However, the two agents have not been compared to each other regarding their anti-arrhythmic properties, nor regarding their effect on ultimate cardiovascular (CV) collapse, or on resuscitability. We therefore determined the effect of magnesium, bretylium, and saline on arrhythmia suppression, time to cardiovascular collapse, and resuscitability, in an animal model of bupivacaine cardiovascular toxicity.

Methods: With institutional Animal Care and Use approval, 15 mongrel dogs (23±3kg) were anesthetized with thiopental sodium (20mg/kg), intubated, and mechanically ventilated. Anesthesia was maintained with halothane 1.0% E.T. in oxygen, muscle relaxation with pancuronium, and ventilation was adjusted based on arterial blood gases. Left carotid and left and right jugular vein catheters were placed. A transverse thoracotomy was performed and the heart suspended in a pericardial cradle. Through a puncture in the left ventricular apex, a catheter was inserted for measurement of left ventricular pressure. The aortic root was then dissected free from the fat pad and encircled with an electromagnetic flow probe. ECG leads II and AVF were also placed. The animals were then randomly divided into three groups. Group 1 animals received a bolus of magnesium sulfate 140mg/kg followed by an infusion of 80mg/kg/hr. Group 2 received a bolus of bretylium tosylate 10mg/kg and an infusion at 4mg/min. Group 3 received a bolus and infusion of saline. Drug concentrations were adjusted to maintain similar bolus volumes and infusion rates. Fifteen minutes after the bolus injection, an infusion of bupivacaine HCl was begun at 1.8 mg/kg/hr and continued until CV collapse (SBP < 50mmHg). At CV collapse, all infusions were terminated and the animals were resuscitated based on ACLS protocol. After ten minutes of resuscitation, if the animal's blood pressure and cardiac output were at or above the pre-resuscitation level without support, the animal was deemed resuscitable.

Data for ECG changes, serious dysrhythmias, and resuscitability were analyzed using chi-square analysis. All other data was analyzed by ANOVA. A $p < 0.05$ was considered statistically significant.

Results: Baseline characteristics were similar in all groups. None of the dogs manifested CV collapse directly from arrhythmias, with all dogs collapsing from cardiac depression and/or electromechanical dissociation. The incidence of P-R interval prolongation after bupivacaine infusion was similar in all groups. The saline and bretylium groups had significantly greater incidences of QRS prolongation and ventricular arrhythmias than the magnesium group. Similarly, the bretylium group had significantly more A-V dissociation, and bundle branch block than the magnesium group. Hypotension and cardiovascular collapse, however, were seen significantly later in the bretylium group, with an average of 57 mg/kg of bupivacaine at collapse, versus 26 mg/kg and 23 mg/kg for the saline and magnesium groups respectively. Blood pressure and pulse could be established in all magnesium dogs and in 4 of 5 bretylium dogs with resuscitation, but in only 3 of 5 saline dogs (not statistically significant).

	Magnesium	Bretylium	Saline
Interval Prolongation (50%)	N	N	N
PR	4	5	5
QRS	1^a	5	5
QT	0^a	1^a	4
PVC's	$0^{a,b}$	5	3
A-V Dissociation	1^b	5	4
Hypotension (SBP < 80)	5.4min	$25.2\text{min}^{a,c}$	8.2min
CV collapse (SBP < 50)	9.6min	$34.0\text{min}^{a,c}$	11.3min
Positive Resuscitation	5	4	3

a: p <.05 vs saline n = 5 for each group
b: p <.05 vs bretylium
c: p <.05 vs magnesium

Discussion: CV collapse from bupivacaine toxicity has been attributed to malignant dysrhythmias or electromechanical dissociation. Both magnesium and bretylium have been suggested as anti-arrhythmics, but their anti-arrhythmic properties have not been compared, nor have they been studied regarding prevention of cardiovascular collapse or resuscitability. Our data suggest that while magnesium masks bupivacaine-induced dysrhythmias better than bretylium, cardiovascular collapse is delayed only by the latter, with more than twice as much bupivacaine needed to induce collapse in the bretylium group. Bretylium and magnesium both significantly prevented QT interval prolongation, a postulated cause of malignant arrhythmias and CV collapse. The basis for prolongation of survival in the bretylium group, therefore, is difficult to explain, although it may be related to its catecholamine-releasing effects. Further studies using a combination of catecholamines and magnesium are underway and may show effects similar to or better than bretylium. For pre-eclamptic patients on magnesium there is no protection from bupivacaine cardiovascular collapse, and although there is no enhancement of cardiovascular depression from the magnesium, there is masking of potentially early warning signs from dysrhythmias. We were able to resuscitate all magnesium dogs using a simple ACLS protocol, although we could not resuscitate 2 saline dogs who received similar doses of bupivacaine. Four of five bretylium dogs receiving significantly more bupivacaine could be easily resuscitated. Bretylium may play an important role in resuscitating patients with bupivacaine CV collapse, even in the absence of overt dysrythmias.

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THE EFFECT OF TENS ON PAIN INTENSITY, PLASMA BETA-ENDORPHIN AND SUBSTANCE P IN CHRONIC BACK PAIN.

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INTRODUCTION:

Trans-cutaneous electrical stimulation (TENS) is an accepted and effective means of chronic pain management, though its precise mechanism of action is largely unknown. Several recent studies have focused attention on the possible role of Substance P (SP) and opioid peptides such as beta-endorphin (BE) in pain relief observed with TENS. Previous studies have shown that SP in plasma and saliva was significantly lower in chronic back pain patients than in normal healthy volunteers (1). Similar results were reported for the SP in the cerebrospinal fluid (CSF) of chronic pain patients (2) and their pilot study indicates that the CSF SP level may be increased to normal levels following TENS treatment (3). Other investigators, using healthy volunteers, have found no significant changes in plasma beta-endorphin levels in response to high or low frequency TENS (4). The type of TENS application (frequency, intensity and modulation) may affect the mechanism of action and the measurable response to TENS therapy. Therefore, the purpose of our study was to determine 1) if there is a measurable response to high frequency TENS as detected by plasma levels of SP and BE as well as subjective pain intensity in a group of chronic back pain patients and 2) to compare two modes of TENS therapy in producing that response.

METHODS:

With the approval of our Institutional Review Board for Protection of Human Subjects, nine chronic back pain patients were enrolled in the study. Blood was drawn and subjective pain intensity was assessed using the Visual Analog Scale (VAS) before and 3 hours after TENS therapy. TENS was applied to the paraspinous lumbar area bilaterally with equipment obtained from Medical Designs (Westerville, Ohio) using two of the available modes of operation: width modulation (W) at rate=85, width=75 and strength duration modulation 2 (SD2) at rate=85, width=100. EDTA plasma was separated and stored at -70° C until analysis. Extraction and radioimmunoassay of SP and BE from plasma were performed according to instructions in the radioimmunoassay kits supplied by Incstar (Stillwater, MN).

RESULTS:

No significant differences were found between the mean pre and post-TENS treatment levels of plasma SP or BE with either of the TENS modulations tested or between the modes. Also, plasma levels of SP and BE were not found to be correlated with the intensity of pain reported using the VAS. The patients were divided into three groups based on their response to TENS therapy. The possible responses are increase, decrease or no change from pretreatment level of plasma neuropeptide levels and VAS score. The individual responses to TENS are indicated in the table. Plasma values which differed by more than 2 standard deviations were considered significantly different. Theoretically, the patients should be equally distributed if there is no trend to their response to TENS. To evaluate if a trend had been established, the chi square test was applied. It was found that TENS decreased VAS score indicating pain relief. However, no significant trend was observed in plasma levels of SP or BE of these patients using either of the TENS modes tested or between the modes.

Table 1: Summary of Individual Responses to TENS in Chronic Back Pain Patients.

TENS MODE	BE	SP	PAIN	RESPONSE
W:3 hrs	1/9	1/9	0/9	increased
	3/9	1/9	8/9	decreased
	5/9	7/9	1/9	unchanged
SD2:3 hrs	2/9	2/9	1/9	increased
	5/9	3/9	8/9	decreased
	2/9	4/9	0/9	unchanged

DISCUSSION:

We did not find a significant trend in plasma SP or BE levels in response to TENS therapy with either of the modulations tested. Neither did we find a significant difference between the two modulations tested. However, VAS scores were lower after 3 hours of TENS treatment demonstrating the pain reducing effects of both modulations tested. Since no trend was found in plasma SP and BE levels post treatment, we conclude that the pain relief experienced was not related to changes in SP and BE and that the changes, if present, were not detectable at the plasma level.

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Title: **Lidocaine and Epinephrine Synergistically Reduce Rat Sciatic Nerve Blood Flow**

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Introduction: Peripheral nerve injury is an infrequent but occasionally devastating complication of regional anesthesia. During regional anesthesia, nerve injury may occur as a direct result of trauma from needles or following ischemia due to nerve compression and edema. Injury may also result from reduction in peripheral nerve blood flow (NBF) caused by local anesthetics or adjuvant vasopressors. Selander et al. (1) have shown that addition of epinephrine to local anesthetics increases the damage caused by intrafasicular injection. Local anesthetics and adjuvant vasopressors may act directly on the smooth muscle of epineurial and endoneurial blood vessels (2) and/or indirectly on the vaso nervorum supplying these vessels to influence NBF (3). The effect on peripheral NBF of topical application of lidocaine (L) and epinephrine (E), alone and in combination, was studied in the rat sciatic nerve.

Methods: After institutional Animal Care Committee approval, sciatic NBF was measured in 30 adult female Sprague-Dawley rats (60 nerves), studied in a randomized blinded experimental design. Animals were fasted overnight and then anesthetized with IP pentobarbitol (50 mg/kg) and diazepam (20 mg/kg) in saline (4). After induction of anesthesia, the animals were placed on a heating pad, and covered to prevent convective heat loss. The hindquarters were shaved and the sciatic nerves were exposed bilaterally by reflection of the overlying muscles. Care was taken to avoid trauma to the epineurial circulation. NBF was measured with a TSI ™ Laser Doppler Flowmeter (LDF) 1 mm probe placed in gentle contact with the sciatic nerve. Optical coupling was provided by a small amount of standard electrode gel. Previous studies have demonstrated good correlation between NBF measured by LDF and other methods (5). The LDF probe was placed under microscopic visualization to prevent it directly overlying epineurial vessels. After five minutes of stable recordings were obtained, 25 µl of the coded experimental solution were applied 0.5 cm proximal to the recording site and continuous records of NBF were made for 40 minutes. At that time, the nerve was washed with 2-3 ml normal saline and the recordings were continued for a further 20 min. Tested were lidocaine (L) 0.5, 1.0 and 2.0%, epinephrine (E) 2.5, 5.0 and 10 µg/ml and L 0.5, 1.0 and 2.0% with E 5 µg/ml (commercial preparation, Astra) and saline (S) control (n=6 nerves/treatment). NBF data were recorded as mV and expressed as per cent of control. Data were analyzed by repeated measures ANOVA with significant interactions investigated by Neuman-Keuls. $p<0.05$ was considered significant.

Results: Changes in NBF produced by L were dose dependent (fig 1). Blood flow reduction was not significant compared to saline for L 0.5% or 1.0% but was significant for L 2.0% at all time periods after 1 min ($P<0.05$). Maximum reduction was seen at all concentrations by five min after application. Average blood flow reduction at 5 min was 7% for L 0.5%, 12 % for L 1.0% and 18% for L 2.0%. No recovery was seen over 60 min despite washout with normal saline at 40 min.

Epinephrine also produced changes in NBF. E 2.5 µg/ml resulted in a transient 20% increase in NBF lasting 2-3 min ($p<0.05$) followed by return to baseline. E 5.0 µg/ml and E 10.0 mcg/ml produced reductions of 20% and 35% respectively ($p<0.05$) which lasted throughout the study. Each of the three concentrations was significantly different from the others. Onset of the effect of E was observed sooner than that of L, with maximum NBF reduction seen at 2-3 min.

Combination of L+E resulted in synergistic reduction of NBF for all drug concentrations ($p<0.05$). For example, whereas L 0.5% was not significantly different from control and E 5 µg/ml reduced NBF by approximately 20%, L+E (0.5% plus 5 µg/ml) resulted in NBF reduction of 60% ($p<0.05$) (fig 2).

Discussion: Small but significant reductions in NBF were seen after topical application of L to rat sciatic nerve. Greater reductions were seen with E, and the combination of L+E resulted in synergistic reduction totalling 60%. The observation that 2.5 mcg/ml E produced a transient rise in NBF suggests that beta effects predominate at the low dose. Meisheri and VanBreeman have previously demonstrated B-receptors in the smooth muscle of rabbit aorta (6). At higher doses, alpha effects predominate. Previous authors have also noted adrenergic nerve terminals located along epineurial and perineurial but not endoneurial blood vessels (3). The 1 mm Laser Doppler probe employed in this study measures blood flow 1 mm into the nerve tissue, approximately the diameter of the sciatic nerve, so should record both epineurial and endoneurial blood flow. The reduction seen after application of L+E is equivalent to that seen when the epineurial circulation is totally stripped from the nerve (5), suggesting that it is epineurial blood flow which was markedly reduced in this experiment.

Local anesthetics might be expected to increase peripheral NBF if they acted only on the smooth muscle of epineurial arterioles. Reduction of metabolic needs of the nerve after blockade and blockade of the vaso nervorum may be responsible for the fall in NBF observed.

Acknowledgment: Support for this study was provided by an American Society of Anesthesiologists Starter Grant Award.

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FIGURE 1

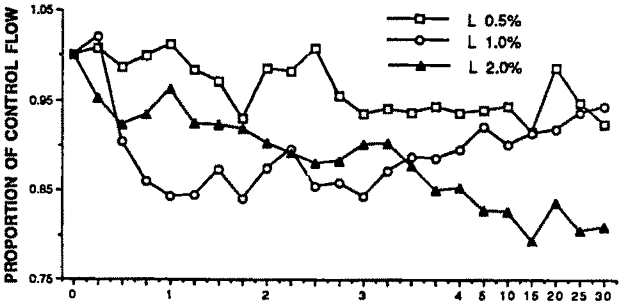

FIGURE 2

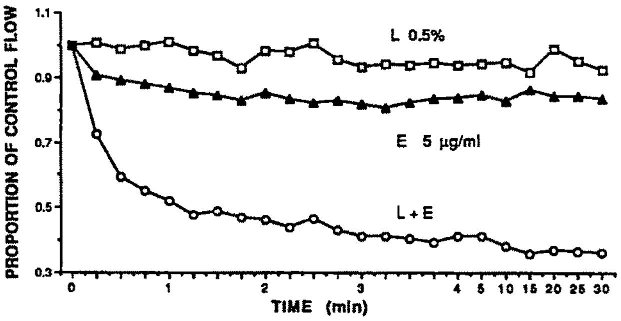

Figure 1: Reduction in NBF after topical application of L 0.5, 1.0 and 2.0%. **Figure 2:** Reduction in NBF after L 0.5%, E 5 µg/ml and L+E.

Title: **The Effect of Local Anesthetics on Sciatic Nerve Blood Flow in the Rat**

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Introduction: Peripheral nerve injury is an infrequent but occasionally devastating complication of regional anesthesia. During regional anesthesia, neural injury may occur as a direct result of trauma from needles or following ischemia due to nerve compression and edema. Injury may also result from reduction in peripheral nerve blood flow (NBF) caused by local anesthetics (LA). Previous investigations of the effect of a number of LA on cutaneous (1) and muscle blood flow (MBF) (2) have shown dose dependent and threshold effects with blood flow either increased or decreased depending upon drug concentration. The effect of LA on peripheral NBF is not well characterized. Acute reduction of NBF has been associated with centrifascicular fiber degeneration in human and animal models (3). LA may act directly on the smooth muscle of epineurial and endoneurial blood vessels (4), and/or indirectly on the vaso nervorum supplying these vessels to influence NBF (5). The effect on NBF of topical application of lidocaine (L), bupivicaine (B), tetracaine (T) and saline (S) control were studied in the rat sciatic nerve.

Methods: After institutional Animal Care Committee approval, sciatic NBF was measured in 27 adult female Sprague-Dawley rats (54 nerves), studied in a randomized blinded experimental design. Animals were fasted overnight and then anesthetized with IP pentobarbitol (50 mg/kg) and diazepam (20 mg/kg) in saline (6). After induction of anesthesia, the animals were placed on a heating pad, and covered to prevent convective heat loss. The hindquarters were shaved and the sciatic nerves were exposed bilaterally by reflection of the overlying muscles. Care was taken to avoid trauma to the epineurial circulation. NBF was measured with a TSI ™ Laser Doppler Flowmeter 1 mm probe placed in gentle contact with the sciatic nerve. Optical coupling was provided by a small amount of standard electrode gel. The probe was placed under microscopic visualization to prevent it directly overlying epineurial vessels. After five minutes of stable recordings were obtained, 25 μl of the coded experimental solution were applied 0.5 cm proximal to the recording site and continuous records of NBF were made for 40 min. At that time, the nerve was washed with 2-3 ml normal saline and the recordings were continued for a further 20 min. Tested were (L) 0.5, 1.0 and 2.0%, (B) 0.25, 0.5, and 0.75%, (T) 0.5 and 1.0% (commercial preparations, Astra) and saline (S) (n=6 nerves/treatment). NBF data were recorded as mV and expressed as per cent of control. Data were analyzed by repeated measures ANOVA with significant interactions investigated by Neuman-Keuls. $p<0.05$ was considered significant.

Results: Both L and B resulted in significant reductions in NBF compared to control S (Table I). Increasing concentrations of L resulted in significantly greater reductions in NBF ($P<0.05$) however, while increasing concentrations of B resulted in progressively less reduction (Table I). NBF from B and L treated nerves was significantly lower for those treated with T or S at all time periods after 5 min. In the doses employed, T resulted in no change in peripheral NBF at any of the time periods measured.

Discussion: In these experiments, L and B reduced NBF in a dose dependent manner. Least effect was seen with T. Johns et al. report similar results for a rat cremaster muscle preparation, although they observed an increase in MBF at very high concentrations of L (10,000 μ/ml) (2). By contrast, skin capillary blood flow (SBF) rose after administration of L and B, in concentrations similar to those investigated here (1). In that preparation, as here, lowest concentrations of B had the greatest effect. As has been noted previously, injection of LA may produce a biphasic response in NBF, with initial vasodilation followed by vasoconstriction. Concentration dependent effects of LA on NBF may result from opposing results of blockade of the vaso nervorum (resulting in vasoconstriction) and blockade of receptors located on the epineural blood vessels (resulting in vasodilation).

The marked difference of the results for NBF from those for SBF points to the difficulty in generalizing about the effects of LA from one organ to another. Thus the frequent use of centrally acting vasopressors or production of a "sympathectomy" to increase "peripheral perfusion" after reimplantation or grafting may have quite different effects on NBF from MBF and SBF.

Acknowledgment: Support for this study was provided by an American Society of Anesthesiologists Starter Grant Award.

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TABLE I: NBF Compared to Control

Study Drug	TIME (min)			
	1	5	10	20
L 0.50%	1.01	0.94	0.94	0.99
L 1.00%	0.84	0.92	0.90	0.92
L 2.00%	0.96	**0.83**	**0.83**	**0.84**
B 0.25%	0.84	**0.65**	**0.69**	**0.67**
B 0.50%	0.91	**0.73**	**0.75**	**0.73**
B 0.75%	0.96	0.90	0.86	**0.76**
T 0.50%	1.04	1.02	1.01	1.08
T 1.00%	1.03	1.05	1.04	1.07

bold face = $p< 0.05$

Title: **Comparison of Pretreatments to Prevent the Cardiovascular Response to ECT**

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Introduction: Electroconvulsive Therapy (ECT), a frequent treatment for patients with psychotic depression, is often accompanied by a massive sympathetic response which may result in life threatening-hypertension, tachycardia and dysrhythmias (1). A number of drug regimens have been suggested for pretreatment to prevent or ameliorate the stress response to the electrical shock and the subsequent seizure (2,3,4). Any effective treatment, however, must not adversely affect the seizure produced or the treatment will not be effective. Additionally, pretreatment should not result in hypotension after ECT. We compared four pretreatment regimens which have been previously advocated: esmolol (E), fentanyl (F), labetolol (Lab) and lidocaine (Lid) to saline (S) control in a double-blind, randomized, cross-over design to determine their effects on cardiovascular changes and seizure duration during ECT.

Methods: After Human Subjects Committee approval and informed consent, seven patients were studied during five sequential ECT treatments given at a rate of 3/wk. All patients were monitored with a precordial stethoscope and pulse oximeter. In addition, continuous records were made of blood pressure (Finapres™ finger blood pressure cuff), ECG, instantaneous heart rate and EEG (1 channel: midline forehead to left mastoid). Following baseline measurements, patients received two coded pre-induction injections. One of the injections contained saline; the other a study drug. F (1.5 µg/kg) and Lab (0.3 mg/kg) were administered 5 min prior to induction and E (1.0 mg/kg) and Lid (1.0 mg/kg) were given 1 min prior to allow for the longer onset times of Lab and F. Induction was with methohexital 1mg/kg and succinylcholine 0.75 mg/kg. Unilateral or bilateral ECT was performed by the psychiatry service using a Thymatron ECT machine (Somatics, Inc.). Systolic, diastolic and mean pressures, heart rate (HR), seizure duration (electric and visible) and time from induction to spontaneous ventilation and awakening were recorded and Rate Pressure Product (RPP) was calculated. Data were analyzed by two-way repeated measures ANOVA with significant interactions investigated by Neuman-Keuls test.

Results: ECT resulted in significant rises in blood pressure (BP) and HR in control studies. Transient rises to as high as 313 mmHg systolic were recorded. RPP increased by an average of 336 per cent ($p<0.01$). BP and HR then fell to near control levels but routinely rose again during emergence sometimes to higher values than seen immediately post-ECT. RPP increased an average of 223% above control, $p<0.01$ (fig 1).

Hypotension or bradycardia was not observed in any patient following drug treatment. Each drug regimen resulted in a significantly decreased blood pressure response to ECT ($p<0.05$), but E and Lab resulted in greater atttenuation than did Lid or F ($p<0.05$). Both Lab and E provided protection against post-seizure tachycardia ($p<0.05$) but neither Lid nor F did so. The RPP increase was lower after E or Lab ($p<0.05$) than after Lid of F (fig 1). Lab provided significant reduction in RPP during emergence ($p<0.05$), but E did not, presumably because of its short half-life. Length of seizure, as determined independently by EEG and gross observation, was significantly decreased by Lab, Lid and F but not by E (fig 2).

No drug treatment affected time from induction to spontaneous ventilation or until the patient was fully awake, and no patient suffered permanent cardiac sequelae following ECT therapy.

Discussion: Pretreatment with Lab and E provided the greatest protection against tachycardia and hypertension following ECT. E reduced seizure duration less than did Lab but a single dose of E provided less protection against the BP/HR rise seen during emergence. Administration of a second dose of esmolol after cessation of the seizure could protect against this second peak.

The second rise in BP and HR observed during emergence in this study has not been described previously, perhaps because monitoring was discontinued prior to that point. In addition, rises in RPP which we observed were higher than that noted by other studies, and higher than those recorded on anesthesia records from our own institution. This may be due to the transient nature of the rise. In this study, continuous finger BPs were recorded whereas intermittently obtained cuff pressures might well miss the peak response.

Increasing the doses of F or Lid might improve their attenuation of the hemodynamic response to ECT but this would likely result in further reduction in seizure length (5). Black et al. found a decrease in seizure length after treatment with approximately 3.0 mg/kg esmolol over 6 min (6). With the smaller dose used in this study, we observed equivalent blunting of the cardiovascular response and seizure duration was not significantly diminished. In balance, pretreatment with esmolol 1.0 mg/kg provided greatest attenuation of the sympathetic response to ECT at the least cost in terms of seizure reduction.

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Figure 1

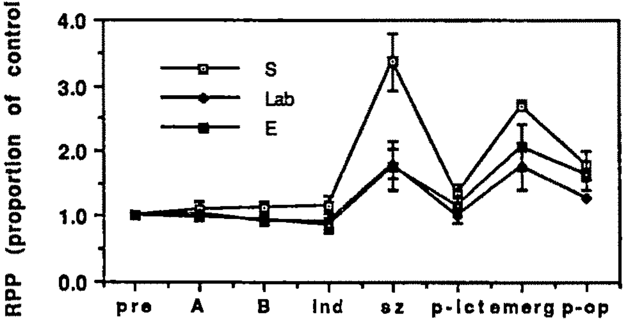

Figure 1: Rate pressure product measured pre-induction, after administration of study drugs A and B, 1 min after induction, immediately post-seizure, the minimum post-ictal, the maximum during emergence and post-operative.

Figure 2

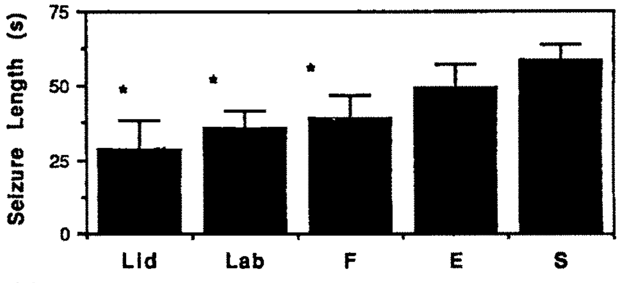

Figure 2: Mean seizure length for patients pretreated with Lid, Lab, F, E or saline. * represents significant difference.

TITLE: **PHARMACOLOGIC BLOCK OF SYMPATHETIC ACTIVITY DOES NOT PREVENT BUPIVACAINE-INDUCED CARDIOVASCULAR TOXICITY IN DOGS**

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Introduction. Long acting local anesthetics, such as bupivacaine, may cause life-threatening cardiac arrhythmias, especially after their inadvertent intravenous injection. Previous studies showing the arrhythmogenic potential of centrally-administered bupivacaine[1] and our own work relating the cardiovascular toxicity of IV bupivacaine to an increase within the left ventricle of effective refractory period (ERP) dispersion[2-3], suggested bupivacaine-induced cardiac arrhythmias may be due to the combined effects of direct myocardial depression and stimulation of sympathetic nervous system activity. The purpose of this study was to assess the efficacy of sympathetic blockade in preventing the cardiovascular toxicity of bupivacaine.

Methods. After institutionally approved consent, adult mongrel dogs weighing 15-25 kg were divided into 4 treatment groups: control (n=12), clonidine (n=6), hexamethonium and atropine (n=6), and metoprolol (n=6). Dogs were anesthetized with pentobarbital (40 mg/kg) and intubated for delivery of 100% oxygen, then given pancuronium bromide (0.15 mg/kg). ECG, strain gauge, and blood pressure monitors were placed, thoracotomy performed, and the myocardium exposed, where 10 electrodes were placed randomly in the left ventricle. After 30-60 minutes stabilization, control ERP dispersion was determined using a Medtronics programmable stimulator. Bupivacaine was then given, as an IV bolus (4 mg/kg over 1 min) followed by slow infusion (0.2 mg/kg/min) to produce steady-state drug levels[2]. ERP's were remeasured and hemodynamic effects (heart rate and arterial pressure) assessed 1-10 min after drug delivery. Ninety min later, dogs were administered intravenously either saline, clonidine (0.3 mg/kg), hexamethonium (10-15 mg/kg) and atropine (0.05 mg/kg), or metoprolol (0.5-1.0 mg/kg). The ability of clonidine to prevent CNS-mediated sympathetic discharge was confirmed in each animal by noting an attenuated hypertensive response to carotid occlusion. Hexamethonium was administered to a dose which no longer produced an acute fall in blood pressure. The beta-1 blocking activity of metoprolol was determined by showing an attenuated tachycardic response to IV isoproterenol (0.08 mg/kg). Thirty min after saline or sympathetic blockade, new base-line measures of ERP dispersion, heart rate and MAP were recorded and effects of a second dose of bupivacaine (4.0 mg/kg, IV over 1 min) assessed. Serum levels of bupivacaine were assayed by gas chromatography on arterial samples drawn 10-12 min after each IV bolus injection of local anesthetic.

Table 1: Cardiac Electrophysiologic Changes after Bupivacaine in Dogs with Sympathetic Block

Pretreatment	ERP Dispersion[a] (base line)	ERP Dispersion (bupivacaine)
Saline	23.8 ± 2.5	75.0 ± 10.6*
Clonidine	36.7 ± 6.7	90.0 ± ---
Hex-Atr	25.0 ± 2.2	74.0 ± 14.0*
Metoprolol	26.7 ± 3.3	93.3 ± 16.7*

*p< .05 vs base-line (repeated measures ANOVA)
[a]Data are mean ± SEM in msec. ERP dispersion was measured 5 min before (base line) and 1-10 min after IV bupivacaine (4 mg/kg bolus over 1 min).

Results. No differences in heart rate, MAP or ERP dispersion were noted between drug groups after the stabilization period. As noted in previous studies[2-3], the initial test dose of bupivacaine (4 mg/kg bolus followed by 0.2 mg/ml/min infusion) caused a significant increase in ERP dispersion in each drug group. The first dose of bupivacaine also caused moderate bradycardia and hypotension. Base-line ERP dispersion after treatment with sympathetic blocking drugs was not different from initial pretreatment conditions. However, the second dose of bupivacaine caused either significant ERP dispersion or cardiac arrhythmias requiring resuscitation in most animals. Pretreatment with sympathetic blockers did not prevent the increase in ERP dispersion after bupivacaine (table 1). ERP dispersion could not be measured in some dogs where resuscitation was required. The incidence of severe arrhythmias was: 2/12 (saline), 4/6 (clonidine), 1/6 (hexamethonium and atropine) and 3/6 (metoprolol). The second administration of bupivacaine also caused hypotension and bradycardia, but no significant differences in heart rate or MAP after bupivacaine were noted between dogs with sympathetic block versus control animals (table 2). Serum bupivacaine levels measured 10-15 min after the IV bolus were similar in each pretreatment group (4-5 µg/ml).

Discussion. Attempts were made to reduce bupivacaine-induced cardiovascular toxicity by pretreating dogs with sympatholytic agents. Various levels of sympathetic inhibition were done, i.e. central inhibition of sympathetic outflow (clonidine), ganglionic block (hexamethonium and atropine) and direct inhibition of cardiac beta-1 receptors (metoprolol). These experiments demonstrate the inability of sympathetic blockers to prevent hemodynamic changes, ERP dispersion or the incidence of cardiac arrhythmias following toxic doses of bupivacaine.

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Table 2: Hemodynamic Changes after Bupivacaine in Dogs with Sympathetic Block

Pretreatment	Heart Rate[a] (bpm)	MAP[b] (mm Hg)
Saline	89.8 ± 4.0*	81.3 ± 5.7*
Clonidine	86.6 ± 8.9	58.2 ± 9.4*
Hex-Atr	86.8 ± 4.1*	74.0 ± 7.7*
Metoprolol	99.0 ± 10.6	48.8 ± 8.8*

*p< .05 vs base-line (repeated measures ANOVA)
[a]Data are mean ± SEM (n) expressed as percent of base-line values. Heart rate and MAP were measured 5 min before and 1 min after IV bupivacaine.

Title: INTERPLEURAL ANESTHETICS IN THE DOG: SYMPATHETIC NEURONAL EFFECTS

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Introduction: Interpleural (IP) local anesthetic (LA) administration has recently emerged as an effective method for pain management. The rather wide distribution of clinical analgesic effects associated with this technique led to the early speculation that the neural blockade may involve somatic (i.e., intercostal nerves), sympathetic afferent (SA), and spinal elements (1). Limited work to date has indicated that the IP technique essentially produces a multi-dermatomal intercostal nerve block with no effect on CNS (spinal) structures (2). However, no studies have been directed toward determining whether IPLA's block sympathetic nerves. The present experiments in dogs, were designed to test the hypothesis that IPLA's may act directly in the thoracic sympathetic chain (TSC) and/or splanchnic nerves thus affecting both SA (sensory) and sympathetic efferent (SE) fibers. We therefore monitored a manifestation of SE blockade (i.e., increased blood flow to abdominal organs and skin and/or decreased cardiac output) as a representation of the presence of SA blockade.

Methods: The experimental protocol was IACUC approved. Adult male mongrel dogs (25-30 kg, n=10) were anesthetized with thiamylal sodium (8 mg/kg) and intubated. The animals were then paralyzed, placed on a ventilator and anesthesia was maintained with 0.8% halothane/50% N_2O/50%O_2. The dogs were prepared with femoral arterial and venous catheters, a left ventricle (LV) catheter (via the carotic artery), a Swan-Ganz (SG) catheter advanced, via the jugular vein, into the right ventricle and pulmonary artery, and an IP catheter (2) positioned on either the right (R) or left (L) side. The dogs were placed in the supine position for study. Regional blood flows were measured employing radiolabeled microspheres injected into the LV catheter. Four determinations were made per study - 2 under control conditions and 1 each at 30 and 60 minutes following injections of the IP catheter with 20 ml 0.5% bupivacaine or saline. Flows were obtained for the right and left forelimb and chest wall skin, liver, spleen, pancreas and right and left kidneys. Cardiac output (CO) values were measured via the SG catheter employing thermodilution.

Results: Arterial PCO_2 (35-40 mmHg), PO_2 (250-300 mm Hg) and mean pressure (90-100 mm Hg) remained constant throughout the experiments. No changes in CO were recorded. Regional blood flow results (means + SE) during control and at 60 min post-drug are presented in fig. 1. In right side injected dogs, significant ($p < 0.05$) changes in blood flow (compared to control) were seen in the liver (86% increase) and pancreas (42% decrease). In both cases, 30 min changes (not shown) were of a lesser magnitude. A similar pattern for the pancreas was observed following left and right side saline and left-side drug injections, indicating that the pancreatic results were not drug related or biased toward one side. Conversely, no flow changes in the liver were observed following saline or left-side LA injections.

Discussion: It is well established that SE blockade to abdominal organs (and skin) increases blood flow to these structures (3). The general lack of any LA-induced blood flow changes in most structures and the absence of a CO effect imply that IPLA's, given in bolus doses approximating those employed clinically in humans, at least do not produce any significant blockade of the TSC. With the animal placed in the supine position, gravity dependent LA pooling over the TSC should have occurred (see ref. 2). The notable exception in the present study is the increased liver flow following right side LA injections. It may be speculated that this is a function of a hepatic splanchnic innervation chiefly coming from the right side (4). Furthermore, these findings suggest that analgesia mediated via SA's, following IPLA administration, may require direct access of drug to sympathetic post-ganglionic nerves such as the greater splanchnic nerve.

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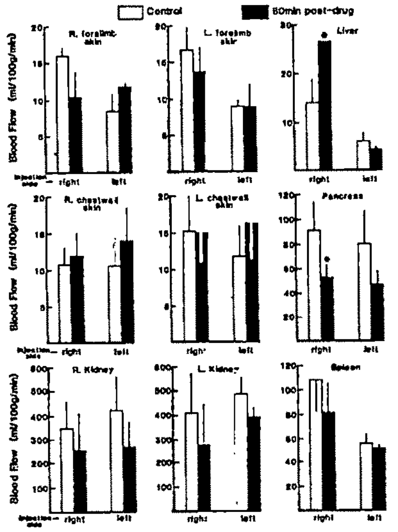

Fig. 1. Regional blood flow changes prior to and 60 minutes following IP administration of 20 ml 0.5% bupivacaine.*$p<0.05$ versus control.

Title: TRANSESOPHAGEAL DOPPLER CARDIAC OUTPUT MONITORING: EVIDENCE FOR IMPROVED ACCURACY DURING AORTIC RECONSTRUCTIVE SURGERY

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Introduction. Cardiac dysfunction results in more than half the perioperative mortality associated with aortovascular surgery.[1] Consequently, efforts are being directed towards developing a continuous, non-invasive monitor of cardiac performance. Due to the effects of atherosclerosis and aortic cross-clamping on aortic flow dynamics, continuous Doppler cardiac output monitoring is not a widely accepted technique during aortic reconstructive surgery. No studies, however, have systematically examined the alterations in Doppler flowmetry caused by atherosclerosis and aortic cross-clamping. This investigation was designed to prospectively evaluate the validity of Doppler transesophageal ultrasonography (TEU) in patients with severe atherosclerosis undergoing aortic reconstructive surgery.

Methods. Doppler TEU was performed in 30 patients scheduled for descending aortic reconstructive surgery using an HIC approved protocol. After induction of general anesthesia and tracheal intubation, Doppler signals were obtained with a 4 MHz esophageal probe (Accucom 2, Datascope Corp.). The transesophageal signals were then calibrated with a suprasternal probe. Aortic cross-sectional area was determined by nomogram based on patient age, height and weight. As a reference standard, thermodilution measurements were obtained at end expiration using room temperature injectate and a dedicated computer (COM-1, American Edwards). Doppler cardiac output and thermodilution cardiac output were defined as the average of 3 consecutive measurements. Data was separated into 3 periods for analysis: 1. preclamp (prior to aortic cross-clamping), 2. cross-clamp (during aortic cross-clamping) and, 3. postclamp (following removal of the aortic cross-clamp). For comparison 20 patients without known aorto-iliac disease undergoing general anesthesia served as the control group. Statistical analysis employed linear regression and descriptive analysis.

Results. Comparison of 506 simultaneous Doppler and thermodilution cardiac outputs are presented in the table below. Coefficient of correlation from the data of the aortic surgery group were superior to those from patients without aortic disease. In the aortic surgery patients the preclamp and postclamp periods had particularly low standard deviation (S.D.) and mean percent error. During aortic cross-clamping, correlations were lower.

Discussion. Our study demonstrates Doppler TEU to be an accurate monitor of cardiac output in patients with severe aorto-iliac disease. The low errors demonstrated by the Doppler technique support its use as a clinical monitor. Our control group has a correlation coefficient not dissimilar to previous investigations.[2] The significantly higher correlations and lower errors seen in patients with aorto-iliac disease suggest that reduced arterial elasticity caused by atherosclerosis may actually limit sources of error in Doppler measurement. Aortic cross-clamping, however, reduces the precision of Doppler TEU. This may reflect disturbances in the relationship between ascending aortic and descending aortic flow. In conclusion, continuous cardiac output monitoring of patients undergoing aortic reconstructive surgery is feasible during the preclamp and postclamp periods. Refinement of technique, however, will be necessary to improve accuracy of Doppler measurements once an aortic clamp is in position.

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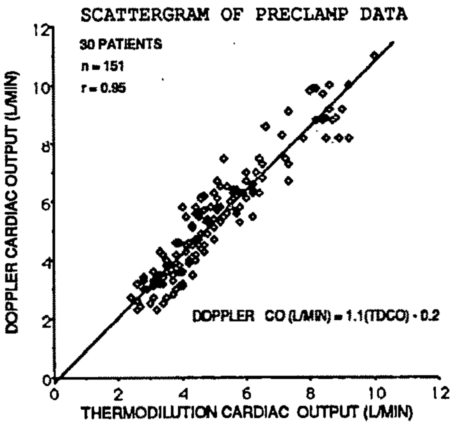
SUMMARY STATISTICS
n = 506

	n	r	S.D.	Mean % Error
PRECLAMP	151	0.95	0.56	9.3
CROSS-CLAMP	97	0.73	1.08	22.3
POSTCLAMP	73	0.82	0.60	10.3
CONTROL GRP	185	0.68	0.92	19.4



Title: **CHANGES OF SERIAL BLOOD GASES DURING BASIC CPR**

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Introduction:

Studies have demonstrated differences between arterial and venous blood gases during CPR without considering the effect of elapsed time variations. We found time related variations during the initial phase of CPR. This experimental study simulates the clinical situation in which effective, basic CPR is initiated immediately at the time of cardiac arrest, prior to the application of advanced resuscitation techniques.

Methods:

Eight mongrel dogs weighing between 17 and 22 kg were utilized under a protocol approved by our institutions Animal Resource Committee. The animals were anesthetized with pentobarbital (25 mg/kg) and maintained on halothane anesthesia. Catheters were placed in both carotid arteries, a peripheral limb vein and the pulmonary artery. A pacing catheter was passed into the right ventricle. After placement of catheters, the dogs were ventilated with a mechanical resuscitator (Thumper, Model 1004, Michigan Instruments) with a rate of 12 breaths/min and a peak airway pressure of 20 cm of water. Baseline blood gases were obtained just prior to the induction of cardiac arrest. A Radiometer Model ABL1 blood gas analyzer was utilized for all blood gas measurements. After fibrillation the Thumper was set to provide 3.0 cm depth of chest compression at a rate of 80 compressions/min. No drugs were administered after the onset of cardiac arrest. Arterial and mixed venous blood gas samples were simultaneously drawn at times of 1,2,3,5,6,10,15 and 20 minutes after the onset of cardiac fibrillation. Blood gas variables of interest were: pH, pCO2, pO2 and the standard base excess (SBE). End tidal CO2 was measured by an in-line capnograph and continuously recorded. Repeated measures statistical analysis was used to determine the significance of the time variation for each variable.

Results:

There are well defined time variations associated with each of the blood gas variables measured here. Figures 1 and 2 show the mean arterial and mixed venous variations for the pH and pCO2 values, respectively. The error bars represent the standard deviation. Figs. 1 and 2 show that the first five minutes after the onset of cardiac arrest demonstrate a markedly different time behavior than the next 15 minutes. Both the arterial and venous pH initially rise and reach maximum values at about 5 minutes. This maximum occurs at nearly the same time that the arterial pCO2 has reached its minimum value (Fig. 2). The repeated measures analysis confirmed that the four curves shown in Figs 1 and 2 require nonlinear terms to adequately represent their time variation. During the first 5 minutes the SBE values (Fig. 3) remain nearly constant, after which a quasi-exponential decrease follows. The nonlinear nature of the SBE variations was supported by the repeated measures analysis. Time variation of the end-tidal CO2 was relatively simple in comparison to the above (Fig. 4). During cardiac arrest the end tidal CO2 was constant. No linear or nonlinear terms were significant in the statistical analysis. Arterial pO2 values were widely variable. Although the arterial pO2 appeared to show a minimum closely followed by a maximum during the first five minutes, the repeated measures analysis found no significant differences between any of the sampling times. Typical values of the arterial pO2 were on the order of 250 mmHg. In contrast, the venous pO2 values were about 60 mmHg at time of arrest and they slowly but continuously decreased to approximately 26 mmHg at 20 minutes.

Discussion:

The experiments described here clearly indicate that rapid physiological changes are occurring during the early stages of basic CPR. As these results were obtained with experimental animals, clinical data should be obtained with patients to determine if such rapid changes in blood gas variables are also occurring during basic CPR in humans. In contrast to the blood gas variables, the end-tidal CO2 remained almost constant during CPR. Several authors have suggested that the end-tidal CO2 provides a measure of the effectiveness of CPR. Since the chest compression and ventilation were not changed during the experiment it was anticipated that the end-tidal CO2 should remain approximately constant. Thus the blood gas variations observed here are related to physiological changes which occur during CPR and not in changes in the chest compression or ventilation patterns.

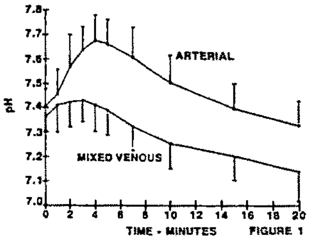

FIGURE 1

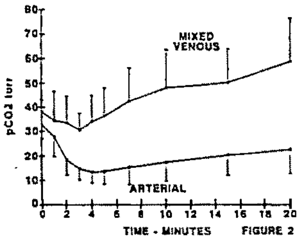

FIGURE 2

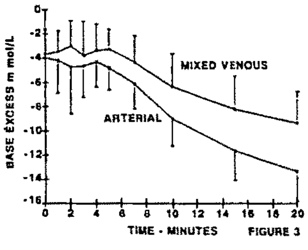

FIGURE 3

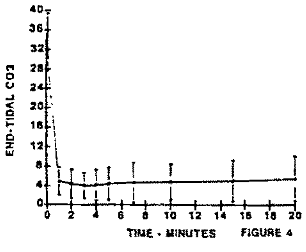

FIGURE 4

Title: ATRACURIUM VS PANCURONIUM INHIBITION OF SUCCINYLCHOLINE FASCICULATIONS

Authors: A.C. Pinchak, Ph.D., P.E., M.D., L.S. Shepard, M.D., L. Patterson, CRNA, J. Hagen, B.A.

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Introduction:

Many factors influence the blockade of muscle fasciculations induced by a bolus of succinylcholine. These include the choice of blocking drug, the waiting time which elapses between the injection of the anti-fasciculation drug and injection of succinylcholine and patient factors, such as age, sex, and specifically weight, etc. In this investigation we studied drug and male vs female differences in the waiting time response curves (percent fasciculation vs waiting time).

Methods:

This study was approved under a monitoring protocol, submitted to the Human Investigation Committee of our institution. A total of 643 subjects were entered into this study and they ranged in age from 9 to 91 years. A standard dose of 1 mg pancuronium or 5 mg of atracurium was administered independent of patient size over the weight range of 50-90 kg. Patients outside this range received a proportioned dose based on their body weight (pancuronium, 0.014 mg/kg and atracurium 0.07 mg/kg). The time was recorded when the non-depolarizing drug was injected and induction proceeded with sodium pentothal (2 to 3 mg/kg). The standard dose of succinylcholine was 100 mg I.V. except for those patients less than 50 kg or greater than 90 kg in weight. Patients outside this weight range received 1.5 mg/kg. After succinylcholine was injected the waiting time was recorded and the patient observed for the presence or absence of fasciculations. Patients were divided into subgroups on the basis of drug (pancuronium, atracurium) sex, age (< 30 yrs; > 30 yrs) and time ($0 < t_1 \leq 3$ min; 3 min $< t_2 \leq 5$ min). A SAS statistical procedure (CATMOD) was applied to these categorical data to determine which factors were of importance in predicting the fasciculation response. The SAS procedure PROBIT then fit curves through the experimental data of percent fasciculation vs waiting time. (Waiting time groups for the PROBIT analysis were 0.0 to 1.5 min, 1.5 to 2.0, 2.0 to 2.5,...4.5 to 5.0 min.) A statistically significant difference between two waiting time curves was determined by a non-overlapping of the 95 percent confidence intervals for each of the two curves in question.

Results & Discussion:

A partial listing of the results from the categorical model (CATMOD procedure) is shown in Table I. The factors having lower values of the probability are those which explain the experimental results. Table I shows that drug, time and sex are important parameters while age is not. None of the interaction parameters (e.g. drug*sex) are listed in this table because they all showed large probability values ($p > 0.11$). The general shape of the PROBIT curves is sigmoid and differences between two curves are usually anticipated in terms of a right or left shift of one curve with respect to the other (see Figs. 1 and 2). To achieve a 50% block of fasciculations with pancuronium longer waiting times (WT_{50}) are required for males as compared to females (2.85 vs 1.68 min.) In contrast, there are no significant differences between the male and female curves with atracurium. Male patients treated with pancuronium have a longer WT_{50} (2.85 min) than male patients treated with atracurium (WT_{50}=1.32 min). The male vs female difference found with pancuronium may be related to the structure of pancuronium molecule. Clinically it is recommended that at least a 4 minute waiting time be utilized with either atracurium or pancuronium for satisfactory anti-fasciculation function with both male and female patients.

TABLE I

Effect	Parameter	Estimate	Standard Error	Chi Square	Prob
Intercept	1	1.174	0.119	97.29	0.0001
Drug	2	0.401	0.112	12.79	0.0003
Age	3	-0.144	0.118	1.50	0.2201
Time	4	-0.699	0.117	35.73	0.0001
Sex	5	0.426	0.116	13.48	0.0002

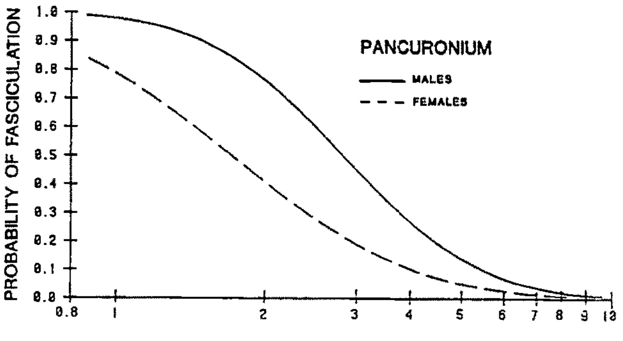

FIGURE 1

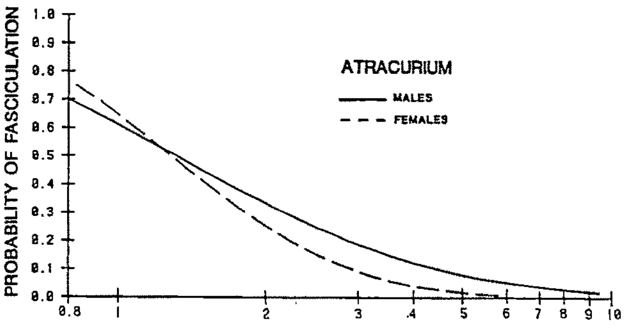

FIGURE 2

Title: ADENOSINE MEDIATES RECOVERY FROM FATIGUE IN ISOLATED RAT DIAPHRAGM

Authors: Anita Polk, BS, Timothy Thurston, MD, and Silvio Glusman, MD, PhD
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Introduction

The elucidation of the mechanism of respiratory muscle fatigue is important in the understanding of the pathophysiology of respiratory failure.

Adenosine, a degradative product of adenine nucleotides, has been shown to increase in the perfusate from contracting muscles. Several studies have shown that at the neuromuscular junction the release of adenosine occurs in parallel with transmitter release.[1,2] We recently demonstrated that aminophylline, an adenosine receptor antagonist, accelerates the recovery from fatigue in the isolated rat hemidiaphragm.

Adenosine deaminase (ADA) is responsible for the deamination of adenosine to inosine, a physiologically less active compound.[3] We investigated the effects of adenosine deaminase on diaphragmatic fatigue to determine the role of adenosine in fatigue and recovery from fatigue in the isolated rat diaphragm preparation.

Methods

After approval by the Animal Care Committee, Sprague-Dawley rats (200-400gms) were anesthetized with ethyl ether and a segment of diaphragm containing parallel fibers was dissected and continously perfused with oxygenated Ringer solution containing d-tubocurarine (6 ug/cc).

The central tendon of the diaphragm was attached to a force transducer and the thoracic cage insertion was fixed to the floor of the recording chamber. A resting tension of 10 gms was applied to the muscle.

The diaphragm was supramaximally stimulated at 0.1 Hz with bipolar platinum field electrodes and twitch tension was recorded with a pen recorder. Diaphragmatic fatigue was elicited by stimulating the muscle at 1.0 Hz for 3 minutes. Recovery from fatigue was studied by analyzing the return of the twitch tension to control values upon returning to 0.1 Hz.

Results

The electrical stimulation of the isolated rat hemidiaphragm at high frequency produces a decrease in the tension that the muscle generates .(Fig1). Upon returning to low frequency stimulation, the twitch tension in the diaphragm gradually returns to control values. The time required for the twitch to recover to one-half of the control tension (t 1/2) after 3 minutes stimulation at 1.0 Hz is 1450 sec.

Adenosine deaminase (1 u/cc) produces a slight increase (13 %) in the twitch tension that the diaphragm generates when stimulated at 0.1 Hz. There is no significant differences in the degree of diaphragmatic fatigue when the diaphragm is stimulated at 1 Hz in the absence or in the presence of adenosine deaminase. However, the recovery from fatigue is greatly accelerated in the presence of adenosine deaminase. (t 1/2 = 101 sec vs. normal t 1/2 = 1450 sec). (Fig 1)

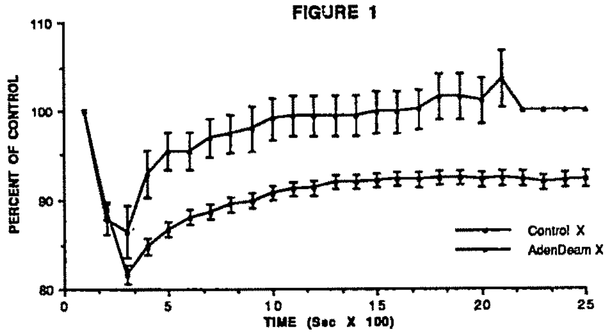

FIGURE 1

Discussion

This study demonstrates that adenosine deaminase, an enzyme responsible for the deamination of adenosine to inosine, a physiologically less active compound, accelerates the recovery from fatigue of the rat isolated hemidiaphragm. This effect of the adenosine degradative enzyme is similar in magnitude and time course to the effect on recovery from fatigue previously described for aminophylline in the same preparation. The present results suggest : 1) that under physiological conditions, adenosine release by the nerve terminals and/or the muscle may be playing the role of a local modulator protecting the muscle by tonically depressing the tension that the muscle generates, and 2) that the effect of aminophylline on recovery from fatigue may be mediated by a mechanism that involves competition with adenosine.

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3. Silinsky, EM: On the mechanism by which adenosine receptor activation inhibits the release of acetycholine from motor nerve endings. J Physiol 346:243-256, 1984

Title: **ARE WE MISSING ANYTHING BY USING DAILY FORMS TO EVALUATE RESIDENTS?**

Authors: S.L. Polk, M.D., M.S.Ed. and P.D. Hodgson

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Introduction: In June, 1988, our Department instituted a daily form (Figure 1) for faculty evaluation of residents, to replace the previously utilized quarterly summary evaluation. The summary form allows a grade of Satisfactory, Satisfactory with Reservations, or Unsatisfactory to be given for each resident by each faculty member in each of the areas covered in the A.B.A. document: Defining Competence in Anesthesiology. The number of daily forms completed by faculty decreased markedly as the year progressed, and so in June, 1989, we distributed the old summary form to faculty, and examined the results of both methods to answer the following questions: How does the information compare, and which system is best?

DATE_____	RESIDENT____________
ROOM _____	ATTENDING___________
EVENTS:	PERFORMANCE:
As Expected [ ]	Below Expectations [ ]
Unexpected [ ]	As Expected [ ]
	Above Expectations [ ]
COMMENTS:	

Figure 1: Daily Evaluation Form

Methods: The daily form is stapled to the anesthesia record and is to be completed at the end of the day by each faculty member who has worked with a resident that day. Faculty members fill out the form by checking the appropriate boxes, and make comments when they feel it is appropriate. Completed forms are collected at a central place in the operating suite, and are reviewed weekly. In this study, forms collected from January through June, 1989 were analyzed. The old summary form, requesting ratings in the areas listed in Table 1, was distributed in late June, 1989. Faculty members were asked to complete and return the forms to us by mid-July, evaluating residents' performance in the past six months (January - June, 1989). The summary form also asks for comments on any residents rated as outstanding or subnormal in any of the categories covered. On July 20, the compiled results of both evaluation systems covering the study period were compared for indications of problems in residents and for the nature of the comments received, as well as for discrepancies in individual faculty member's evaluations and comments or in their participation in the evaluation process.

Results: In the time period studied, 156 daily forms were received, evaluating 21 of 23 residents. Fifteen of 26 clinical faculty members who were working during the entire six month period completed at least one daily form, with five faculty members contributing 80% of them. Sixteen faculty members completed the summary form for the 23 residents. Four faculty members completed some daily forms but not the quarterly form. Five faculty members completed the summary form but no daily forms. Four faculty members completed neither form, and twelve participated in both systems.

Table 1 summarizes the number of residents cited as having weaknesses in each evaluation process, as identified by more than one negative comment (daily forms) or average rating of less than satisfactory (summary form). Two of the twenty-three residents had no daily evaluations during the six month period; both were on rotations outside the operating room, taking minimal call. One was judged to be substandard and one excellent on the summary form. Each resident cited on the daily form was also cited on the summary form, but the reverse was not true. Weaknesses in other residents were noted on the summary form which had not been noted on the daily forms during the study period, but these had been mentioned on daily forms in the previous six months and on previous summary forms.

Table 1: Weaknesses Noted in Residents

	Number of Residents Cited	
Weak Area	**Daily**	**Summary**
Knowledge	0	4
General medical judgment	0	4
Pre-op care	4	4
Postop care	0	3
Intraoperative management	1	2
General preparation skills	0	1
General anesthesia skills	0	1
Regional anesthesia skills	0	0
Special procedures skills	0	0
Essential characteristics*	1	3
Important characteristics*	1	6
Overall clinical competence	1	3

*As defined in the ABA definition of clinical competence.

Discussion: In this Anesthesia Department the daily evaluation system has met with less than 100% participation on the part of the faculty, as did the summary system in the past. We found during the six month period that the summary form pointed out some weaknesses in some residents which were not identified on the daily forms. In each instance, these areas had been identified during the previous six months. There are several possible explanations for this variance: faculty did not care to repeat similar comments day after day (there were, though, other instances when faculty reported similar deficiencies throughout the entire year); that the problems had been resolved but were mentioned on the summary form because isolated incidents make a lasting impression, which the resident has difficulty "living down"; that a "halo effect" causes summary evaluations to reflect reputation and rumor rather than personal experience. We favor one of the latter two explanations, and we contend that the daily system provides the most accurate current picture of resident performance. It appears that incidents which stand out in the residents' performances, positive or negative, are commented upon, and that the low rate of form completion by most faculty members reflects absence of noteworthy incidents, positive or negative. The overwhelming opinion of our evaluation committee is that the daily system promotes early intervention and correction for residents who demonstrate weaknesses, and that the summary system does not provide the information and documentation nearly so well or on such a timely basis.

There are two minor issues which the daily system does not resolve. Some faculty refuse to participate in either system. We can only conclude that it is because they don't feel strongly enough about any resident to do so. The daily system cannot change that, nor do we believe another system can. Secondly, daily forms have not proven useful to evaluate residents working outside the operating rooms (e.g., pain clinic). We wonder about the validity of the information provided on the summary forms about these residents, when they may be evaluated by faculty who have not worked with them during the period in question. We need to examine this further.

In summary, extra data provided on summary forms does not appear to add current information to the daily forms for residents in the operating room, but reflects historical information about a resident's past performance. We believe the daily system provides more timely and valid information than do the summary evaluation forms in our program. Better faculty participation is desirable, in order to be more certain that we are not overlooking continuing problems on the assumption that they have been resolved.

TITLE: DESMOPRESSIN IN VIVO AFFECTS VISCOELASTIC WHOLE BLOOD COAGULATION

AUTHORS: S. Porter, M.D.; C. Taneyama, M.D.; H. Goto, M.D.; K. Goto, M.D.
AFFILIATION: Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas 66103

Introduction: Desmopressin (DDAVP) liberates Factor VIII from vascular endothelium and may enhance platelet function.[1] DDAVP is used to reduce blood loss and transfusion in the surgical patient.[2] The Sonoclot Coagulation Analyzer (Sienco, Morrison, CO) measures viscoelastic whole blood coagulation (VEC), allowing rapid specific analysis of the etiology of coagulapathy.[3] We investigated the effects of DDAVP on the measured parameters of VEC.

Methods: After giving informed consent, 16 patients undergoing orthopedic surgical procedures were studied. Preoperative whole blood samples were obtained for platelet count (PLT), protime (PT), partial thromboplastin time (PTT), fibrinogen (FIB), and VEC, and bleeding time (BT) was also measured. Each patient received 0.3 mcg/kg DDAVP over 30 min. One hour later, all measurements were repeated. VEC was analyzed by immersion of a vibrating probe in the recalcified whole blood sample. Resulting viscous impedance is quantitated as a plot of voltage versus time. VEC measurements included 1) onset time (OT), 2) primary slope (PS), 3) secondary slope (SS), and 4) peak interval (PI) (Fig 1).

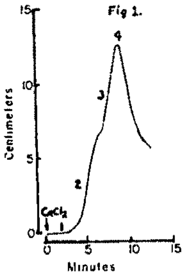
Results: PT and PTT were not significantly different after DDAVP administration. Platelet count and fibrinogen were significantly decreased after DDAVP. Bleeding time was also significantly shortened after DDAVP administration (Table 1). VEC onset time was significantly shorter after DDAVP administration (Fig 2).

Discussion: Onset time and PS reflect initial recalcification and fibrin monomer formation, which requires circulating coagulation factors. SS and PI indicate platelet deposition and clot retraction. Shortened OT after DDAVP without changes in PS, SS, or PI confirm[1] that DDAVP may act by transiently increasing circulating coagulation factors in the surgical patient rather than by enhancing platelet activity. This effect can be assessed by measurement of viscoelastic whole blood coagulation.

Table 1. (All values are mean ± SEM)

PARAMETER	PRE-DDAVP	POST-DDAVP
PT	12.1±0.7	12.8±0.7
PTT	30.7±2.8	30.8±3.7
BT	8.63±0.7	6.33±0.5
PLT CT	309K±84K	242K±62K*
FIB	254 ±61	175 ±42

*P<0.05



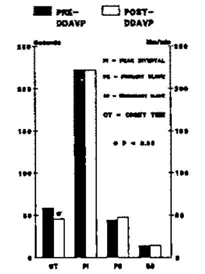


FIG 2 EFFECT OF DDAVP ON SONOCLOT

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3. Saleem A, Blifeld C, Saleh SA, et al. Viscoelastic measurement of clot formation: A new test of platelet function. Ann Clin Lab Sci 13:115–124, 1983.

TITLE: THE EFFECT OF INTRATHECAL MORPHINE ON POSTERIOR TIBIAL SSEP MORPHOLOGY IN ANESTHETIZED MAN

AUTHORS: S. S. Porter, M.D.; M. A. Asher, M.D.; M. Calvillo
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Introduction: Intrathecal opiates used during extensive spine surgery facilitate deliberate hypotension, reduce anesthetic requirements, and provide postoperative analgesia. Intraoperative somatosensory evoked potentials (SSEP) are an adjunctive monitor for detection of neural injury. Interpretation can be affected by a variety of anesthetic agents alone or in combination (1). High doses of systemic narcotics do not alter the latency or amplitude of SSEP's (2), nor does intrathecal morphine in the awake, unpremedicated individual (3). The influence of intrathecal morphine on interpretation of SSEP's in the surgically anesthetized patient has not been previously examined.

Methods: After informed consent and institutional approval were obtained, eighteen patients scheduled to undergo extensive spine surgery requiring SSEP monitoring were selected for study. Anesthesia was induced with thiopental 4-6 mg/kg, pancuronium 0.1 mg/kg, and intravenous fentanyl 100 ug, and maintained with isoflurane 1.0% in 100% oxygen. Baseline SSEP were obtained using bilateral posterior tibial nerve stimulation at 3X motor threshold at 4.13 stimuli/second. 250 averages were acquired with bandpass filters at 20-300 Hz. Recording electrodes were placed at Cz (vertex) referenced to FPz (forehead). In the prone position, all patients then received 0.025 mg/kg of preservative-free morphine intrathecally using a 22-25 gauge spinal needed inserted aseptically at L4-5. Serial SSEP were then obtained at 5,30,60, and 90 minutes after injection. Anesthetic administration was maintained constant in all patients, and MAP >20% of baseline was treated with intravenous labetalol or sodium nitroprusside.

Amplitude of the P1-N1 cortical response and latencies of P1 and N1 peaks were tabulated. Results were analyzed using analysis of variance for repeated measures, and the Newman-Keuls post-test for significant interactions. A P value of <0.05 was considered statistically significant.

Results: There were no significant changes in latency of either the P1 or N1 response throughout the period of study. There was also no significant alteration in amplitude of the cortical SSEP after morphine injection at any time (See table).

Discussion: These results suggest that the use of intrathecal morphine in the patient undergoing extensive spine surgery does not interfere with the interpretation of SSEP morphology. There is no indication that subarachnoid morphine enhances the dose-dependent depression of SSEP amplitude characteristic of isoflurane, or produces other effects on SSEP when used in the patient anesthetized with isoflurane and low-dose fentanyl.

References:

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PARAMETER	BASELINE	5 MIN	30 MIN	60 MIN	120 MIN	P
LATENCY P1 (mSEC)	38.0±0.9	38.1±1.1	37.9±1.0	38.2±1.0	38.6±1.1	NS
LATENCY N1 (m SEC)	52.6±1.6	54.5±2.3	51.9±1.6	53.0±2.1	52.4±1.5	NS
AMPLITUDE P1-N1 (uV)	2.16±0.4	1.77±0.3	1.77±0.4	1.57±0.3	1.73±0.3	NS

(*All values are mean ± SEM)

Title: A NEW HIGH EFFICIENCY BLOOD WARMER FOR CHILDREN

Authors: R.G. Presson, Jr., M.D., K.A. Haselby, M.D., E. Barnett, R.N.
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Introduction: Massive hemorrhage can result in hypovolemia and hypothermia if infusion rates and warming of transfused blood products are inadequate. A device such as the Rapid Infusion System™ (Haemonetics Corp, Braintree, MA) can deliver a high flow rate with efficient warming,[1] but the large priming volume (750 ml for the R.I.S.™) makes it unattractive for pediatric use. We recently evaluated a new high efficiency blood warmer for children, the System 250™ (LEVEL 1 Technologies Inc., Marshfield, MA), and compared this device to a conventional single-channel dry wall electric blood warmer (American Pharmaseal Model DW1000A, Valencia, CA), equipped with a blood recipient set containing an 80 μm filter (Fenwal 4C2138, Travenol Laboratories, Deerfield, IL). Like the conventional warmer, the System 250™ has small priming volume (50 ml vs. 80 ml). In contrast, the System 250™ employs a single-channel countercurrent heat exchanger warmed to 40°C by a circulating water bath.

Methods and Materials: Flow rates were measured with packed red blood cells diluted to an hematocrit of 30% with normal saline. Output temperature was measured with normal saline infused at 20°C. Fluids were pressurized with an inflatable bag connected to an orthopedic tourniquet box. Pressure across the system was measured with two transducers; the first measured the inflating pressure of the blood bag, and the second measured pressure at the tip of the delivery system. Flow through the warmers was initiated over a series of inflating pressures. After pressure readings had stabilized, flow rates were calculated from the time to infuse 100 ml of fluid measured with an electronic balance and a stopwatch. The temperature of the fluid exiting the warmer was measured with a thermistor placed 1 cm distal to the second pressure transducer. The lowest stable temperature was recorded at each flow rate. All measurements were made in duplicate. Results were analyzed for significance with a one-way nonlinear analysis of covariance (significance at $p<.01$).[2]

Results: Flow rate was significantly better through the System 250™ compared to the conventional warmer at all pressures (figure 1). The flow rate of blood at 300 mmHg was approximately 500 ml/min for the System 250™ compared to 250 ml/min for the conventional warmer. The output temperature of the System 250™ was also significantly higher than the conventional warmer at all flow rates (figure 2). At a flow rate of 400 ml/min, the output temperature of the conventional warmer fell to 30°C while the System 250™ was able to warm fluid from 20°C to 33°C at flow rates up to 750 ml/min.

Discussion: Like conventional blood warmers, the System 250™ has a simple set up and low priming volume yet delivers nearly double the flow rate for a given pressure while providing a significantly higher output temperature.

References:
1. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW, Starzl TE, Winter PW: Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985: 64:888-96.

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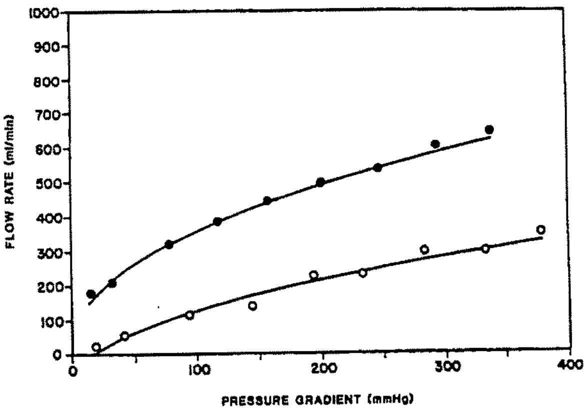

Figure 1. flow rate of diluted red blood cells (● System 250™, o standard warmer).

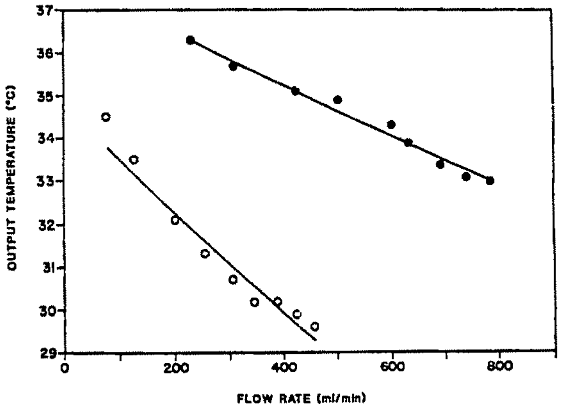

Figure 2. output temperature of crystalloid (● System 250™, o standard warmer).

Title: MYOCARDIAL EFFECTS OF ISOFLURANE VERSUS HALOTHANE IN PATIENTS WITH STEAL-PRONE CORONARY ANATOMY

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INTRODUCTION: Inhalation anesthetics are commonly used as adjuncts to high dose narcotics in patients undergoing coronary artery bypass grafting (CABG). Recent studies have shown that isoflurane (ISO) but not halothane (HAL) can cause coronary vasodilation and myocardial flow redistribution (coronary steal), that can cause ischemia (1). Thus, there has been concern over the safety of using ISO especially in patients with steal-prone coronary anatomy. Experimental and clinical data, suggest that coronary steal and ischemia is unlikely to occur, if coronary perfusion pressure is maintained (2). The present study was, therefore, performed to compare the myocardial hemodynamics and metabolic effects of ISO and HAL in patients with steal-prone coronary anatomy undergoing CABG.

METHODS: The protocol was approved by the Human Studies Committee and written informed consent was obtained from all patients (pts). A total of 16 pts with steal-prone coronary anatomy, defined as a total or near total occlusion in one coronary artery which is supplied distally by collaterals from another coronary artery with a 50% or greater stenosis (3) were studied and randomly assigned to receive ISO or HAL after fentanyl (50 mcg/kg) induction. All pts (mean age 63.5 yrs) had ejection fraction > 45%, were maintained on their preoperative cardiac medication, and were premedicated. Radial artery, pulmonary artery and coronary sinus (CS) catheters were inserted prior to anesthesia. The CS Baim catheter was inserted via the right internal jugular and advanced into the great cardiac vein (GCV) under fluoroscopy. Transesophageal Echocardiography (TEE) was used in 13 of the patients (5 HAL and 8 ISO). Hemodynamics, CS and GCV blood flows, and arterial CS and GCV blood samples for lactates and O_2 content, along with 7-lead ECG (13 pts) were obtained at 4 events; namely postinduction (control-event 1), preincision (10-20 min on ISO or HAL - event 2), poststernotomy (25 - 35 min on ISO or HAL - event 3), and 60 minutes on ISO or HAL (event 4). The inhalation anesthetic was started after intubation and was maintained at inspiratory concentration of at least 0.5 MAC. Heart rate was controlled around 60 bpm by atrial pacing throughout the study. Diastolic pressure was maintained within 10% of control levels with phenylephrine as required. Myocardial ischemia was defined as the development of new wall motion abnormalities (TEE), myocardial lactate extraction (MLE) of less than 10% or lactate release and/or new ST segment changes greater than 0.1 MV or T wave inversion. One way analysis of variance was used to compare parameters between the groups and chi square test was used tc compare the incidence of ischemia between the two groups

RESULTS: Hemodynamic and metabolic data are presented in the table. There were no significant differences between the two groups at any of the events except for global myocardial O_2 consumption (MVO_2) which was different between the two groups at control and throughout the study. A progressive decrease in global (CS) and regional (GCV) MLE was observed during ISO. New ischemia was observed at event 3 (n=2) and event 4 (n=2) in the ISO group and at event 2 (n=3) and event 4 (n=2) in the HAL group. One ischemic episode was detected by ECG, TEE and MLE (event 4 HAL group) and the rest were detected by MLE only. None of the patients sustained an intraoperative myocardial infarction.

DISCUSSION: Under the conditions of the study, myocardial ischemia occurred during the administration of either inhalation anesthetic in patients with steal-prone coronary anatomy, but the incidence of ischemia between the groups did not differ. The difference in global MVO_2 between the two groups was not due to the inhalation anesthetic used since it was also present at control. The data suggest that ischemia in these patients is most likely due to factors other than coronary steal, i.e. coronary vasodilation and myocardial flow redistribution, since regional to global flow ratio did not change and ischemia occurred with either inhalation anesthetic.

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TABLE (mean±SD)

		Event 1	Event 2	Event 3	Event 4
BPd	I	68±9	66±10	69±8	61±6
(mm Hg)	H	68±11	67±10	68±8	68±8
CO	I	4.7±.9	4.3±.7	4.0±.5	4.1±1.2
(L/min)	H	4.6±1.0	4.1±1.0	3.9±.9	4.2±1.0
GCV/CS Flow	I	.49±.18	.51±.17	.52±.19	.47±.18
Ratio	H	.49±.20	.48±.18	.45±.17	.50±.23
Global MVO2	I	9.0±2.6*	8.1±2.9	8.2±2.7	8.3±2.7*
(ml O2/min)	H	13.7±4.1*	11.8±4.6	10.8±2.7	12.0±2.4*
Global MLE	I	40±13	32±14	23±11	22±14
(%)	H	27±20	22±20	31±18	24±15
Regional MLE	I	46±18	32±14	26±14	24±19
(%)	H	33±22	28±23	36±19	28±13

* P<.05 statistical difference between I and H groups

THE VALSALVA MANEUVER: PERIPHERAL CIRCULATORY CHANGES AND EFFECTS UPON FUNCTION OF THE PULSE OXIMETER

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Introduction Pulse oximetry has been utilized for monitoring maternal oxygen saturation during labor. However, it frequently fails to perform as expected during the second stage of labor. When signal quality for the Nellcor N-100 pulse oximeter falls below certain limits, the gain control is reset at the next highest level and the instrument attempts to recapture and analyze pulse and light wavelength data. If the signal remains poor the instrument continues to re-set the gain at higher and higher levels. This sequence of software and hardware adjustments is referred to as "auto-fallback mode" (AF mode). During this time, the "Pulse Search" light is illuminated and the display screen either frozen or blank, effectively interrupting of transmission of oxygen saturation data by the pulse oximeter. Part I and Part II of this study measured the frequency and duration of AF mode relative to Valsalva maneuvers in pregnant and nonpregnant subjects. Part III consisted of noninvasive vascular measurements in nonpregnant volunteers performing the Valsalva maneuver.

Methods This study was approved by the institutional Human Investigation Committee. **Part I:** Eight pregnant patients in the lithotomy position with adequate epidural analgesia who were actively pushing during the late second stage of labor were studied. Pulse oximetry data were recorded using a pulse oxmeter and a strip recorder (Nellcor N-100; Nellcor, Inc., Hayward, CA). Other than placement of a disposable sensor on the toe, there was no interference with the patients and expulsive efforts were coached in a routine manner by the delivery room staff. Several Valsalva maneuvers in rapid succession separated by a single breath are referred to as a salvo.

Part II: Pulse oximetry measurements were made in nine healthy nonpregnant volunteers performing the Valsalva maneuver. This group differed from the pregnant patients in these respects: four males were included; the Valsalva maneuver was performed in the supine rather than the lithotomy position; volunteers did not receive epidural analgesia; and subjects were allowed to rest between each Valsalva maneuver rather than performing a salvo.

Part III: Venous impedance plethysmography (VIPG) and pulse volume recording (PVR) was used to noninvasively evaluate the Valsalva maneuver in nine healthy nonpregnant volunteers (8 males, 1 female). Subjects were studied in the supine position and did not receive epidural analgesia. Each subject performed a series of Valsalva salvos, similar to the pregnant subjects in Part I. An IPG-100 plethysmograph (Codman and Shurtlett, Inc.; Randolph, MA) was utilized to assess venous capacitance of the leg as subjects performed three Valsalva maneuvers in rapid succession. Following this, a pulse volume recorder (Life Sciences, Inc.; Greenwich, CT) was utilized to evaluate arterial pulse volume amplitude in the toe and the calf in the resting state and in association with a salvo of Valsalva maneuvers.

All data are reported as means ± SEM where appropriate. Statistical significance is defined as $P < 0.05$ and was computed using Student's t-test.

Results Part I: The pulse oximeter reverted to auto-fallback mode in association with the Valsalva maneuver in all nine pregnant patients studied. In a total of 130 Valsalva maneuvers, reversion to AF mode occurred during 108 (83%). In 42 salvos, AF mode occurred in 41. Once the signal was lost, it took 10.6 ±1.5 s (range 0-45) for recovery following the last Valsalva maneuver in a salvo. The mean duration for interruption of normal oximetry function during each salvo was 17.1 ± 1.5 s. The mean duration of the salvos was 28.9 ±0.76 s. Thus, the oximeter tended to reverted to AF mode during 59% of each salvo.

Part II: The Valsalva maneuver resulted in the pulse oximeter reverting to AF mode in 8 of 9 nonpregnant volunteers. In these 8, 33 of 35 separate Valsalva maneuvers triggered AF mode. Volunteers differed significantly from pregnant subjects in the time from initiation of a Valsalva maneuver to reversion to AF mode by the oximeter. This delay was 3.3 ± 0.54 s in pregnant subjects and 5.9 ±0.78 s in volunteers ($P< 0.007$).

Part III: The Valsalva maneuver in volunteers was associated with a 54.6 ±5.2 % decrease in pulse volume amplitude from baseline. A rapid decrement in pulse volume amplitude occurred within 2-3 heartbeats after initiation of the Valsalva maneuver and persisted for the duration of the Valsalva maneuver. The point at which the pulse volume amplitude decreased to less than twice the variation in the baseline amplitude (signal-to-noise ratio less than 2:1) was identified as the time of signal failure. This value, 5.7 ± 0.6 s, was not significantly different from the time to AF mode in nonpregnant subjects, but was significantly prolonged ($P > 0.008$) compared to pregnant subjects. Occlusive VIPG studies demonstrated no increase in venous blood volume in any subject during any 10-second Valsalva maneuver.

Discussion This study demonstrates that the pulse oximeter is unable to consistently provide meaningful oxygen saturation data during a Valsalva maneuver. The pulse volume recordings indicate a 50% decrease in cardiac output as the cause for the signal failure during Valsalva maneuvers. This is the same decrement in cardiac output found in an earlier study of the Valsalva maneuver using thermodilution techniques (1). The shorter time to signal failure for pregnant patients compared to nonpregnant subjects may relate to partial impairment of venous return by the gravid uterus while in the lithotomy position.

These findings have implications for obstetric practice. The time honored practice of strenuous pushing during the second stage may in fact impose an additional hypoxic burden upon the fetus due to decreased uterine blood flow. While readily tolerated by the vigorous fetus, this additional insult may result in severe distress in a compromised fetus. Further study is warranted to assess the risk/benefit ratio of Valsalva maneuver under such circumstances.

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Title: **HEMODYNAMIC EFFECTS OF MECHANICAL VIBRATION CHEST PHYSIOTHERAPY**

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Introduction:

The use of mechanical vibrator chest physiotherapy (MVCP) has been shown to be safe and effective in clearing secretions and opening atelectatic lung areas.(1,2) Although the technique has become popular in intensive care medicine we could find no data about the effects of MVCP on hemodynamics.

Methods:

We studied 12 patients in a multidisciplinary ICU, all of whom required mechanical ventilation and right heart catheterization for their management. The admitting diagnoses included liver transplantation, pneumonia, pulmonary edema, sepsis and post-op cardiac surgery. Four patients were receiving inotropic support.

Cardiac index, SVRI, PVRI pulse and BP were measured in each patient during a standard 30 minute period of MVCP. Measurements were made before therapy, during treatment at the 15 minute mark, at the end and one hour after completion of therapy. Results were analyzed using one way analysis of variance. This study was approved by the institute's Human Ethics Committee and a signed consent was obtained from each patient.

Results:

There were no significant changes in any of the parameters measured during the study period, and all patients remained hemodynamically stable, even those requiring inotropic support at the time of study.

Discussion:

Mechanical vibration chest physiotherapy produces no deleterious effects on the cardiovascular system in ICU patients, even those receiving inotropic support.

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Title: EPIDURAL ANESTHESIA IN ASTHMATIC PARTURIENTS
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INTRODUCTION In asthmatic parturients undergoing cesarean section (CS), epidural anesthesia is commonly administered in order to avoid general anesthesia and its associated complications. However, there are certain major concerns regarding the use of regional anesthesia in asthmatic patients.[1] 1) The high levels of sensory block can cause respiratory discomfort in the supine position; 2) the high levels of motor blockade interferes with the motor power of the abdominal and thoracic muscles affecting the patients' ability to cough and clear secretions; 3) the high levels of sympathetic blockade of lungs can precipitate bronchospasm due to unopposed parasympathetic activity. The purpose of this retrospective study was to evaluate the incidence of the above complications and the safety of the use of epidural anesthesia in asthmatic parturients undergoing cesarean sections.

Methods and Materials During 1986 and 1987, a total of 61 parturients with asthma were admitted. Of the 61 patients,19 were admitted with exacerbation of asthma with dyspnea, tachypnea, productive cough and wheezing.In these patients, the initial therapy consisted of hydration, O2 by nasal cannulae, and terbutaline 0.25 mg subcutaneously. When the response to initial therapy was inadequate, intravenous aminophylline and steroids were administered.

In patients receiving epidural anesthesia for CS,the epidural catheters were inserted in the L_{2-3} or L_{3-4} interspace in the usual manner. After a test dose 20-25 ml of either 2% lidocaine with 50-100 ug of fentanyl or 3% 2-chloroprocaine was administered in 5 ml increments to obtain a T_2- T_4 sensory block. Left uterine displacement was maintained and O2 was administered via face mask. The end-tidal CO_2 levels and O2 saturation were continuously monitored throughout the procedure. After the delivery of the baby, midazolum 1-2 mg was administered for sedation.

In patients receiving general anesthesia, preanesthetic medication included bicitra 30 ml orally. After preoxygenation, anesthesia was induced with ketamine 1 mg/kg or pentothal 4 mg/kg. Succinylcholine, in doses of 1.5mg/kg, was used to facilitate tracheal intubation. Cricoid pressure was applied from the beginning of induction and maintained until the correct position of the tracheal tube was verified. Anesthesia was maintained with N_2O and O_2 (50:50) with isoflurane 0.5-1%. Fentanyl, in doses of 50-100 ug, was administered after the delivery of the baby. Lidocaine, 75-100 mg, was administered prior to extubation.

Results: Of the 61 patients, 29 underwent cesarean section(CS) and 32 women delivered vaginally. Among the 29 patients who underwent CS, 24 received epidural anesthesia and 5 patients received general anesthesia.

Among the 24 patients receiving epidural anesthesia for cesarean section, 8 patients had exacerbation of their symptoms during labor. In six of these patients, there was hypoxemia as evidenced by a pa O_2 ranging from 66-79mmHg on room air at the time of admission. All these patients subsequently improved with the initial treatment. A sensory level of T_2-T_4 was obtained in all the patients . None complained of dyspnea. The ABG values(with patients breathing 02 via face mask) were recorded in 15 patients during the procedure and these were within acceptable limits(Table1). None required additional bronchodilators during the procedure.

In the general anesthesia group (n = 5), ketamine was used for induction in 3 patients. In the remaining 2 patients, pentothal was chosen as they had severe preeclampsia in addition to asthma. Transient bronchospasm developed in these two patients and also in one of the patients who received ketamine, following tracheal intubation. This disappeared with the administration of isoflurane.The ABG values (FI 02 0.5) are given in table1. There were no significant cardiac dysrrhythmias with the use of isoflurane in patients who received aminophylline, terbutaline or both.

Conclusions The results indicate that in asthmatic parturients undergoing cesarean section, epidural anesthesia with high levels (T_2-T_4) of sensory blockade does not cause dyspnea, bronchospasm, hypoxemia or hypercarbia. Furthermore, our results indicate that it can be safely administered in both asymptomatic patients with history of asthma and in symptomatic patients with acute exacerbation of asthma during labor after the institution of appropriate therapy.

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Table 1 Data from asthmatic parturients undergoing cesarean section under epidural and general anesthesia.

	EPIDURAL (n =24)	GENERAL (n =5)
Dyspnea	absent	-
Bronchospasm	absent	n = 2
End-Tidal CO2>36mmHg	none	none
O2 saturation<97%	none	none
pH	7.42 ± 0.04	7.42 ±0.03
paO_2 (mmHg)	143 ± 33	220 ±20
pa CO_2 (mmHg)	32 ± 2.5	30 ±1.8

TITLE: TRANSFER AND CONJUGATION OF MORPHINE IN THE HUMAN PLACENTA

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Introduction: The isolated human placental cotyledon has been used in vitro to study placental transfer and metabolism of many drugs (1). Since the human placenta is used, clinical correlation may be better than in animal studies. This study describes the transfer of morphine across the human placenta in a previously validated in vitro perfusion model(1).

Methods: The perfusion chamber consisted of top and bottom water jackets (37 deg C) enclosing the housing for the placenta. A 7.5-cm OD hole in this housing permitted mounting and isolation of the cotyledon. The perfusion biophase consisted of NaCl, KCl, NaH_2PO_4 $MgSO_4$, $CaCl_2$, D-Glucose, $NaHCO_3$ and albumin. Maternal and fetal sides of the placenta were perfused using separate volumetric perfusion pumps at 700 ml/hr and 350 ml/hr respectively with no recirculation. Term placentas were collected from healthy patients following vaginal delivery or cesarean section. The fetal vein and artery were cannulated immediately and the placenta was mounted and perfusion started. Special blunt needles were inserted into the maternal surface of the cotyledon. The perfusate contained antipyrine for the calculation of placental antipyrine clearance (Cl). Only experiments from placentas with the Cl > 2 ml/min were included. The following experiments were conducted: 1) (n=4) The maternal perfusate contained 50ng/ml of morphine, 2) (n=2) The maternal perfusate contained 50ng/ml of morphine 3- glucuronide (m-3-g), 3) (n=2) Fetal perfusate contained 50ng/ml of m-3-g. Maternal and fetal samples were collected at 10, 20, 30, 40, 50, 60, and 70 min from the start. Maternal samples were collected from the placental well and fetal samples from the fetal vein. Free morphine (FM) was measured using radioimmunoassay (Coat-a-Count, Diagnostic Products, Los Angeles, Ca). The concentration of conjugated morphine (CM) was measured by first incubating the sample with a mixture of β-glucuronidase and sulfatase (Biotechnology Systems, Boston, MA) and then measuring the total morphine concentration in the hydrolyzed sample (2). CM was also measured in the presence of the β-glucuronidase inhibitor saccharolactone 5mg/ml (n=1).

Results: Free Morphine crossed the placenta achieving a fetal/maternal ratio of 0.18 (Fig 1). The FM concentration of the fetal samples remained stable throughout the study period. The fetal samples contained insignificant amounts of CM. On the maternal side, CM was detected (Fig 2) in all the samples. When β-glucuronidase activity was blocked with saccharolactone, in vitro hydrolysis of conjugated morphine did not occur. In experiment 2, negligible amounts of m-3-g were found on the fetal side and in experiment 3, insignificant amounts of CM were detected on the maternal side.

Discussion: Data show that human placenta allows passage of only unconjugated morphine. Conjugated morphine undergoes only restricted transfer from mother to fetus or vice-versa. This finding is in agreement with data from in vivo animal experiments (3). Data also show that the human placenta is capable of producing a morphine conjugate which requires UDP-glucuronyltransferase enzyme. Thus, the placenta provides an additional extrahepatic site for morphine inactivation in pregnant women. The restricted passage of m-3-g across the placenta may lead to accumulation of significant amounts of that compound in the fetus following prolonged maternal exposure to morphine.

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FIG 1:

FREE MORPHINE: MATERNAL VS. FETAL

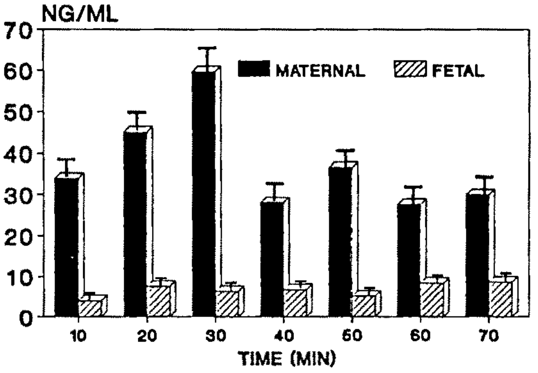
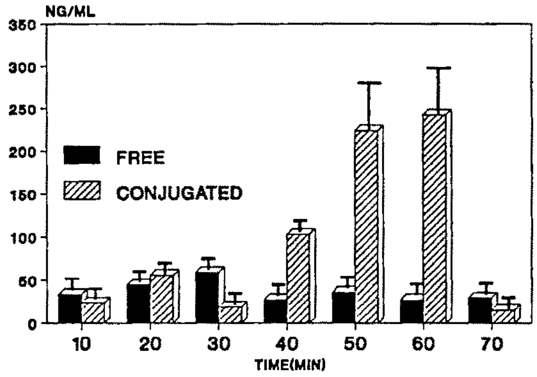


FIG 2:

MATERNAL MORPHINE: FREE VS. CONJUGATED



Title: EFFECTS OF AGE OR NITROUS OXIDE ON THE MAC OF DESFLURANE

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Introduction. Desflurane (previously I-653) is a new volatile anesthetic which has an anesthetic potency one fifth that of isoflurane in swine (1). We report the Minimal Alveolar Concentration (MAC) of desflurane in surgical patients and the influence of either age or concurrent administration of nitrous oxide upon MAC.

Methods. We studied thirty six ASA I or II patients scheduled for elective surgery after obtaining their informed consent and approval from our Institutional Review Board. Patients aged 31-65 were prospectively divided into two anesthetic groups: desflurane/oxygen (n=11) or desflurane/nitrous oxide(60-70%)/oxygen (n=16). Patients aged 18-30 (n=9) received only desflurane/oxygen anesthesia. No premedication was given. Anesthesia was induced by administration of slowly increasing concentrations of desflurane in oxygen or oxygen/nitrous oxide *via* face mask. During induction, signs of airway irritation were recorded by the anesthesiologist. Tracheas typically were intubated without muscle relaxants, but if necessary succinylcholine, 1 mg/kg iv, was given. After intubation, mechanical ventilation was initiated to maintain a $P_{ET}CO_2$ at 30-35 mmHg. Esophageal temperature was maintained above 35°C.

The "Up-Down" method of Dixon (2) was used to prospectively determine the test concentration of desflurane for each patient. The end-tidal concentration of desflurane was allowed to stabilize for ten min at the test concentration before surgical incision. Airway concentrations of desflurane, CO_2, and N_2O were continuously measured using infrared absorption analysis. MAC was determined, as previously described, using purposeful movement of any extremity within one min of incision as a positive response (3). Following determination of MAC, anesthesia was maintained with desflurane. Narcotics and muscle relaxants also could be administered at the discretion of the responsible anesthesiologist. On awakening from anesthesia, and on the first and third post-operative days, the patient was interviewed to assess the subjective side effects of desflurane. Interviews and airway observation data were analyzed using Kruskal-Wallis ANOVA, with significance set at the $p < 0.05$.

Results. Desflurane appears to be a mild airway irritant. Sixty one percent of all patients had secretions requiring aspiration; 50% of subjects coughed more than once; 34% had some degree of laryngospasm, and 29% had some degree of breath-holding. The incidence of these effects did not differ by age or the presence of N_2O. The MAC of desflurane was 7.25 ± 0.0(SD)% in patients 18-30 yr and 6.0 ± 0.29% in patients 31-65 yr. The addition of 60% N_2O in the older group reduced MAC to 2.85 ± 0.65%. Patients receiving desflurane with N_2O had less postoperative memory of the anesthetic induction than those given desflurane alone. Overall, 68% of patients reported no subjective impairment of mentation as early as 20 min postoperatively. Those receiving N_2O reported less impairment than those receiving desflurane alone.

Conclusions. Desflurane is less potent than other available volatile anesthetics. Nonetheless, a MAC of 6 - 7.25% still permits administration of high concentrations of oxygen. Desflurane provided clinically acceptable anesthesia with or without the use of adjuvant drugs in patients aged 18 - 65 yr.. The addition of N_2O seemed to improve patient acceptance of induction with desflurane.

This study was supported in part by Anaquest, Inc., and the Anesthesia Research Foundation.

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Title: IS THERE BIOEQUIVALENCY BETWEEN TWO SUCCINYLCHOLINE PREPARATIONS?

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Introduction. The depolarizing muscle relaxant succinylcholine has been used since 1951. Recently, the FDA has received reports that question the bioequivalency of succinnylcholine as supplied by different vendors, i.e., Quelicin, Abbott; Anectine, Burroughs Wellcome. There have been no comparative studies of the two products in the literature, however, and no data on their bioequivalency is available from published reports. Because the reported instability of succinylcholine may present problems of manufacture and storage, we tested the hypothesis that Quelicin and Anectine at four different institutions are bioequivalent.

Methods. After approval from each of the four institutions we obtained informed consent from 120 patients–aged 18 to 70, ASA classes I through II–scheduled to undergo surgery with the aid of general endotracheal anesthesia. The patients were randomized into two groups equal in demographics, age, and concomitant disease. After preoxygenation and prefasciculation with dTC, 3 mg, anesthesia was induced with thiamylal or thiopental, 3-6 mg/kg. Adjuvants such as fentanyl, midazolam, and intravenous lidocaine were used as the anesthesiologist providing care for the patient deemed appropriate. Succinylcholine, 1.5 mg/kg, was given by means of a syringe labeled with a prearranged coding system known only to the pharmacist. A sealed code was provided to each investigator which could have been broken in the event of a serious or unexpected adverse reaction. Neuromuscular function was recorded with the aid of a Datex train-of-four monitor. Data collected for each patient included the concomitant or maintenance medications, the time from administration of succinylcholine to intubation, the percent muscle twitch depression at intubation, the subjective evaluation of intubation, the time to recovery of twitch height, the total succinylcholine dosage, and the investigator's rating of adverse experiences. The data were analyzed by analysis of variance, and the power of this study to detect a 20% difference in time to intubate or quality of conditions for intubation between succinylcholine preparations was 90%.

Results. Patients in the two groups were equal from a demographic, age, and concomitant disease standpoint. There was no statistically significant difference between groups when the action of Quelicin and Anectine were compared from time of administration of succinylcholine to successful intubation and in all other areas of comparison (table).

Table (mean + 1 SD)

	Quelicin	Anectine
Time to successful intubation	95.6 ± 29 s	98.1 ± 33 s
Time to 80% recovery of twitch depression	669 ± 404 s	647 ± 328 s
Total dosage	112 ± 34 mg	108 ± 21mg
# of Patients with flaccid vocal cords	56/59	56/58

Discussion. Because of its ready hydrolysis and need for refrigerated storage, succinylcholine is a less than optimal drug to manufacture and to handle. Our study indicates that when the products from two companies are handled identically at the hospital or surgicenter, no statistically significant clinical or neuromuscular effect can be measured when two preparations of succinylcholine are compared. Thus, differences in effect or in action of the preparations must be considered to rest either in the ability of an institution to successfully store the preparations, or in subjective factors in individual patients and anesthetists.

Title: HEMODYNAMIC CONSEQUENCES OF DOXACURIUM IN ABDOMINAL AORTIC SURGERY

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Introduction Doxacurium chloride (DC) is a long-acting benzylisoquinoline neuromuscular blocking agent that has been reported to be devoid of cardiovascular side effects.[1] Its ED_{95} is 30 µg/kg, and it did not release histamine in doses as high as 80 µg/kg. The cardiovascular stability of doxacurium has been demonstrated in healthy patients, and in patients with cardiovascular disease.[2,3] The present study examined the hemodynamic effects of DC in patients undergoing abdominal aortic surgery.

Materials and Methods Ten ASA Physical Status III and IV patients scheduled to undergo elective abdominal aortic aneurysm repair were included in the study. The study protocol was approved by the institutional research administrative committee, and each patient gave written informed consent. All patients had reasonable exercise tolerance and were hemodynamically stable. Exclusion criteria included alcoholism, known drug abuse, unusual sensitivity to neuromuscular blocking agents, and major systemic diseases. Monitoring included axillary arterial and pulmonary arterial catheters. Following the induction of anesthesia with 30 µg/kg of fentanyl and 0.1 mg/kg of diazepam, orotracheal intubation was facilitated with succinylcholine, 1 mg/kg. Five minutes after intubation, baseline hemodynamic parameters were recorded (T0). Doxacurium chloride, 50 µg/kg, was then given as a rapid bolus through a central venous line. Hemodynamic parameters were recorded at 2 (T2), 5 (T5), and 10 minutes (T10) following the bolus of DC. Data were analyzed using repeated-measures ANOVA and Dunnett's test, and $P < 0.05$ was considered statistically significant.

Results Nine patients completed the protocol without incident. The only statistically significant changes were: a slight increase in mean arterial pressure (MAP) at T10, and slight decreases in cardiac output (CO) at T2 and T5. No changes occurred in heart rate (HR), mean pulmonary artery (MPAP), pulmonary capillary wedge (PCWP), or right atrial (RAP) pressures. Results are summarized in the table.

Within 2 minutes of receiving DC, 1 patient had severe arterial hypotension associated with cutaneous flushing and pulmonary arterial hypertension, but without any change in heart rate. The hypotensive episode lasted 3 minutes, and was treated with $CaCl_2$, 500 mg, and ephedrine, 40 mg, IV. The patient suffered no sequelae. The data from this patient were excluded as he did not complete the study protocol.

Discussion Long-acting nondepolarizing muscle relaxants currently in clinical use are associated with side effects, such as vagolysis or histamine release. This study demonstrated cardiovascular stability following bolus administration of DC in 9 of 10 patients. The statistically significant changes seen in MAP and CO were not clinically important since they represented changes of less than 20% from the baseline values.

The patient who developed severe systemic arterial hypotension and cutaneous flushing in response to DC probably exhibited an anaphylactoid response to doxacurium chloride. There had been no previous exposure to the drug. For the purposes of this discussion, this idiosyncratic response will not be considered, since it has been previously reported.[4]

Initial clinical studies have suggested that doxacurium is potent, predictable in its dosing, and devoid of cardiovascular effects in healthy patients.[5] In patients undergoing elective cardiac surgery, Stoops et al[6] reported no clinically significant hemodynamic changes after doxacurium administration during sufentanil-midazolam anaesthesia. The current study differs from that of Stoops et al in that fentanyl-diazepam anesthesia was used, but is similar in that no clinically significant changes were found.

Doxacurium chloride merits further investigation to determine its pharmacokinetic and pharmacodynamic profile in the presence of major systemic diseases, such as hepatic and renal dysfunction. The actual incidence of idiosyncratic hypotensive responses to DC will become evident as it is administered to larger sample sizes than those previously reported. In conclusion, DC appears to be free of cardiovascular side effects in the majority of patients undergoing abdominal aortic surgery.

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Table Means ± Standard Deviation N=9

	T0	T2	T5	T10
HR (bpm)	62±25	58±20	55±18	56±19
MAP (mm Hg)	84±22	82±22	80±22	90±23*
MPAP (mm Hg)	20±4	18±4	18±5	19±4
PCWP (mm Hg)	13±5	13±5	13±4	14±6
RAP (mm Hg)	11±4	10±3	10±3	10±3
CO (l/min)	4.8±2.0	4.1±1.7*	3.9±1.4*	4.0±1.6

*$P < 0.05$ compared to T0

Title: THE INFLUENCE OF PERICARDIAL CONSTRAINT ON INTRAOPERATIVE RIGHT VENTRICULAR FUNCTION

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Introduction The pericardium is a non-distensible collagenous structure that encapsulates the heart. In patients without pericardial disease, the effects of pericardiotomy on diastolic compliance and ventricular function are controversial. The right ventricle may be particularly susceptible to the effects of pericardial constraint. The present study examined the effects of pericardiotomy on right ventricular function using the rapid-response thermistor pulmonary artery catheter (RRPAC).

Methods Twenty-four patients undergoing myocardial revascularization surgery, without evidence of pericardial pathology, were studied. Written informed consent was obtained from each patient and the study protocol was approved by the institutional research administrative committee. Premedication consisted of morphine 0.1 mg/kg and scopolamine 0.005 mg/kg intramuscularly. Cardiac medications were continued until the time of surgery. In addition to standard monitoring, each patient had a radial arterial catheter and RRPAC inserted prior to the induction of anesthesia. The pressure lines were connected to aneroid-calibrated transducers zeroed to the level of the right atrium. Anesthesia consisted of fentanyl (100 mcg/kg), diazepam (0.1–0.5 mg/kg), pancuronium (0.1 mg/kg), and 100% oxygen. After tracheal intubation, the patients were mechanically ventilated to maintain normocarbia. An additional 15 mcg/kg of fentanyl was administered to each patient prior to sternotomy in order to ensure an adequate depth of anesthesia. Hemodynamic data were collected during brief periods of apnea at end-expiration. Thermodilution measurements were obtained in triplicate using iced injectate. The American Edwards REF-1 Cardiac Output Computer measured cardiac output (CO), heart rate (HR), and right ventricular ejection fraction (RVEF). From these data, the computer calculated stroke volume (SV), right ventricular end-diastolic volume (RVEDV), and right ventricular end-systolic volume (RVESV). Pressure data were recorded on a multi-channel recorder for analysis of systolic blood pressure (SAP), diastolic blood pressure (DAP), mean arterial pressure (MAP), systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), mean pulmonary arterial pressure (MPAP), and central venous pressure (CVP). Baseline measurements (PRE) were recorded following sternotomy and dissection to the pericardium, but prior to pericardiotomy, with the sternum fully retracted. The pericardium was then fully opened by a midline incision from the superior pericardial reflection on the aorta, to the diaphragmatic border. At the level of the diaphragmatic border, transverse incisions were made and the pericardial edges were suspended to the chest wall. Following this, the full set of thermodilution and hemodynamic measurements was repeated (POST). Statistical analysis was performed using a paired Student's T-test, and significance was defined as $p < 0.05$.

Results All patients completed the experimental protocol. Following pericardiotomy, several significant changes were observed. There were increases in SAP (4.5%), MAP (3.7%), SPAP (11.8%), CO (9.1%), SV (6.9%), and RVEDV (7.6%), while CVP decreased (8.6%). No significant change was seen in RVEF. Results are summarized in the table.

Discussion The effects of pericardial constraint on ventricular performance are controversial. Mangano found no significant effects of pericardiotomy on left ventricular performance.[1] However, the right and left ventricles differ in chamber shape, wall thickness, and intracavitary pressure. These differences may make the right ventricle more susceptible to pericardial constraint. In dogs, the right ventricle is more sensitive to increases in pericardial pressure than the left.[2] In humans, studies of pericardial constraint have utilized measurements of pericardial pressure. However, these measurements are technically difficult and subject to positional artifact. The present study utilized measurements of right ventricular volumes to assess the response to pericardiotomy. In the current study, pericardiotomy augmented right ventricular diastolic filling and stroke volume, indicating an overall improvement in performance. Additionally, the decrease in CVP following pericardiotomy supports the concept of pericardial constraint.

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Table
Means ± S.D. N = 24

	PRE	POST	P-VALUE
HR (bpm)	64.8±10.8	56.2±12.0	NS
SAP (mm Hg)	119.6±16.3	125.0±19.7	<.005
DAP (mm Hg)	57.3±6.9	58.9±7.8	NS
MAP (mm Hg)	78.1±7.8	81.0±9.9	<.02
SPAP (mm Hg)	29.7±20.3	33.2±20.3	<.01
DPAP (mm Hg)	15.0±9.7	15.7±9.7	NS
MPAP (mm Hg)	19.9±13.1	21.5±13.0	NS
CO (l/min)	3.3±0.9	3.6±0.9	<.01
RVEF	0.43±0.15	0.44±0.16	NS
SV (cc)	61.5±19.8	65.8±20.7	<.05
RVESV (cc)	98.3±61.5	106.3±67.5	NS
RVEDV (cc)	155.1±68.2	166.9±72.7	<.05
CVP (mm Hg)	7.7±3.5	7.0±3.3	<.02

TITLE: CONTINUOUS INFUSION OF FENTANYL AND MIDAZOLAM FOR CARDIAC SURGERY

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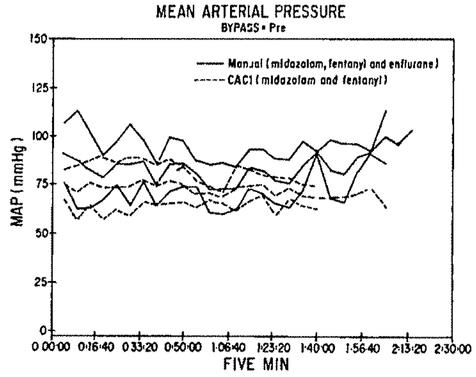
Introduction: Continuous infusion of intravenous anesthetic drugs is a rational alternative to the induction and maintenance of general anesthesia with large bolus doses.[1] Knowledge of infusion rates and knowledge of desirable target plasma levels for satisfactory depth of anesthesia has been an impediment to the widespread use of continuous drug infusion. The purpose of this study was to determine the infusion rates required to maintain adequate anesthetic depth (stable hemodynamics) with the continuous infusion of midazolam and fentanyl during cardiac surgery.

Methods: Following institutional approval, twelve patients electively scheduled for coronary artery bypass graft surgery gave informed consent to receive anesthesia by a pharmacokinetic model-driven computer-assisted continuous infusion (CACI) of midazolam and fentanyl.[2] Patients were premedicated with morphine and diazepam or with methadone and scopolamine. Induction was accomplished by administration of midazolam until both consciousness and lid reflex were lost, then fentanyl was added to blunt hemodynamic responses. Vecuronium (0.1 mg/kg) was given for muscle paralysis. Fentanyl and midazolam were continuously administered to keep the HR and MAP within 20% of baseline values. Mean loading doses and infusion rates for the two drugs were computed from the infusion profiles generated by the computerized infusion device. Six patients given anesthesia with CACI were compared to a group (n=6) of patients induced with midazolam (0.2 mg/kg) and maintained with intermittent bolus of fentanyl and enflurane to keep hemodynamic ±20% of baseline.

Results: Patients whose infusion data are in the table were asleep within two minutes of starting the midazolam infusion and no patient had recall of intraoperative events. The mean loading dose for midazolam was 0.08 mg/kg and was infused at approximately 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until the initiation of cardiopulmonary bypass (CPB). Fentanyl was given as a loading dose of 7 μg/kg and infused at approximately 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until cardiopulmonary bypass (CPB). During CPB, midazolam and fentanyl were infused at 0.40±0.12 and 0.04±0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. Following CPB, midazolam and fentanyl were infused at approximately 0.52±0.32 and 0.10±0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. Note that continuous infusion with CACI produced a smoother HR and BP course than intermittent bolus use of fentanyl and enflurane. (Figures)

Discussion: Continuous infusion of midazolam, for induction and maintenance of hypnosis and amnesia, and fentanyl, for analgesia, provide dependable total intravenous anesthesia during cardiac surgery in patients receiving a hypnotic premedication. A computerized infusion device was used for this investigation to facilitate the calculation of loading and infusion doses for commercially available infusion pumps (e.g. Bard Infuser). The average infusion rate data provided (table) can be readily applied to these manually-controlled infusion pumps. The infusion rates must be continuously titrated based according to patient responsiveness, as is common practice with inhalational anesthesia; thus, these data serve as starting doses for the 3 distinctive phases of (preop, intra and post CPB) of cardiac anesthesia.



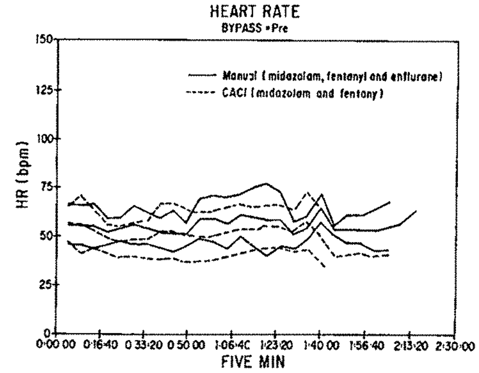


Table Loading and Infusion Dosing During Cardiac Surgery

Midazolam

	Load	Infusion
Pre CPB	0.08 mg·kg	0.5 $\mu g/kg^{-1} \cdot min^{-1}$
CPB		0.40±0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Post CPB		0.52±0.32 $\mu g.kg^{-1} \cdot min^{-1}$

Fentanyl

	Load	Infusion
Pre CPB	7 μg·kg	0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$
CPB		0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Post CPB		0.10±0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$

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TITLE: FLUMAZENIL ANTAGONIZES MIDAZOLAM-INDUCED RESPIRATORY RATE DEPRESSION.

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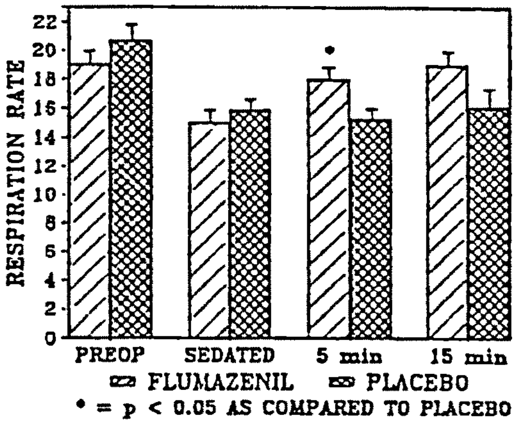
Introduction: Flumazenil is a specific benzodiazepine antagonist acting on the GABA-Benzodiazepine receptors of the central nervous system. Induction of anesthesia and deep sedation with intravenous midazolam is associated with respiratory depression.[1] This study is to determine if flumazenil will antagonize midazolam-induced respiratory rate depression.

Methods: Fourteen unpremedicated ASA class I-II male patients scheduled for elective surgery under regional anesthesia and intravenous sedation were entered into this study. Each patient consented to this study, which was approved by our Institutional Review Board. Prior to regional anesthesia the patient's respiratory rate was recorded. Following regional anesthesia all patients received deep midazolam sedation which was maintained until the end of surgery. On arrival in the recovery room all patients were deeply sedated with midazolam. All patients were pain free. Respiratory rate was again recorded. In a randomized double-blind fashion patients were then given either placebo or 0.2 mg of flumazenil at 60 second intervals until the patient's sedation was fully reversed or 5 doses of test drug had been given. At 5 and 15 minutes after test drug was begun the respiratory rate was again recorded. Data were tested for statistical significance with unpaired t-test between placebo and flumazenil at each time interval.

Results: The flumazenil and placebo groups were demographically similar. All patients were deeply sedated before test drug administration. Five minutes after the test drug was begun the flumazenil group's respiratory rate changed from 15.1 ± 0.8 to 18.1 ± 0.8 ($p < 0.05$), a statistically significant increase. All were awake and talking. At 15 minutes post-flumazenil the respiratory rate was the same as preoperative. The maximum dose was 1.0 mg. The placebo group remained sedated and the midazolam-induced respiratory rate depression continued.

Discussion: Respiratory rate of spontaneously breathing patients can be depressed with intravenous midazolam. Flumazenil titrated at the rate of 0.2 mg flumazenil per minute will antagonize midazolam-induced respiratory rate depression.

Reference: Anesthesiology 1980;53:494-499.



TITLE: A PHARMACOKINETIC STUDY OF ATRACURIUM IN ANHEPATIC PIGS

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INTRODUCTION: Atracurium besylate (ATR)is an intermediate-acting nondepolarizing muscle relaxant, with the unique feature of rapid spontaneous chemical inactivation at physiological pH and temperature by Hofmann decay. Additional degradation pathways include a nucleophilic substitution reaction and ester hydrolysis. It has been suggested that organ-based metabolism or excretion, tissue uptake and/or a chemical reaction not evident in vitro may account for more than one-half of the clearance of ATR (1,2). Since renal failure has little or no effect on its plasma kinetics, the main organ of metabolism may be the liver.

This study was undertaken to investigate the pharmacokinetic profile of ATR in an anhepatic pig model, to elucidate the contribution of the liver to its clearance.

METHODS: The study was approved by the Animal Care Committee of this institution. Fourteen pigs weighing 17-29 kg were premedicated with im ketamine 15 mg/kg and atropine 0.6 mg/kg. The trachea was intubated without the use of muscle relaxant and anesthesia was maintained with isoflurane 1-2% in O_2 and N_2O. A jugular venous catheter was inserted for fluid and drug administration and central venous pressure monitoring. Placement of a femoral arterial line facilitated measurements of the mean arterial pressure and sampling for blood gas analysis and ATR levels. Lactated Ringer's solution was infused as required for hemodynamic stability (CVP $\geq$ 10 mmHg) and the arterial pH maintained within the range of 7.35-7.50 with boluses of $NaHCO_3$ and controlled ventilation to a $PaCO_2$ of 30-40 mmHg. The rectal temperature was recorded at 35.5-37.5°C.

A single iv bolus of ATR (0.5 mg/kg or 1 mg/kg) was given and blood samples drawn every 5 mins for 30 mins, then every 10 mins for 30 mins and finally at 20 min intervals for a total of 120 mins. A portocaval shunt was performed and the liver excised. A second iv bolus of ATR was then given; with sampling and measurements made as previously described. Each 3 cc sample of heparinized blood was placed on ice, followed by centrifugation at 0° C. The plasma was separated, acidified and immediately stored at -70°C. The clearance (CL), volume of distribution (Vdss), mean residence time (MRT), and elimination half-life (t1/2) were calculated using standard techniques. Data are expressed as mean ±S.E. For statistical comparison an unpaired t-test was used to incorporate all data sets, with a p value of < 0.05 considered significant.

RESULTS: Hepatic (control) data were obtained in 14 pigs and anhepatic data in 9 pigs. The plasma decay curves were nonlinear, with a steeper ~~initial phase,~~ followed by an apparent linear first-order disposition phase (Fig.1). The CL was similar during the control and anhepatic phases in each pig with a significant increase in the Vdss and t1/2 during the anhepatic phase, but no change in the MRT (Table 1).

DISCUSSION: Contradictory results have been reported on the effects of impaired hepatic function and biliary excretion on the elimination of ATR (2). Our findings are consistent with those of Pittet in which the clearance of ATR remained unchanged before, during and after their "anhepatic" phase of liver transplantation in pigs, as determined by a constant rate infusion producing no significant change in the plasma levels of ATR (3). An increased Vdss in our model, which may have resulted from expansion of the plasma volume with dilution of plasma constituents, would explain the increase in the t1/2B of this drug. It would appear that liver uptake, biotransformation and excretion does not play an important role in the plasma clearance of atracurium.

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Fig 1 PLASMA ATRACURIUM LEVELS

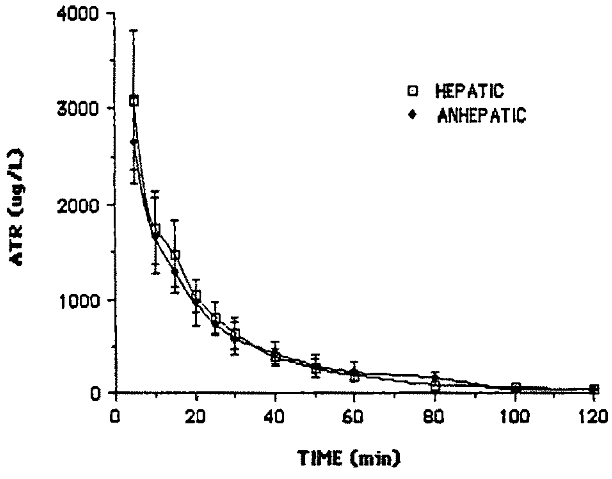

Table 1

	Hepatic	Anhepatic	p
n	14	9	
CL(mL/min/kg)	21.1±2.46	25.0±3.69	NS
t1/2 (min)	20.7±1.56	27.7±2.79	0.03
MRT (min)	27.7±2.07	26.5±2.38	NS
Vdss (mL)	525±51.0	762±114.8	0.04

TITLE: **JUGULAR VENOUS OXYGEN SATURATION AS AN ESTIMATE OF CEREBRAL BLOOD FLOW DURING CARDIOPULMONARY BYPASS**

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Introduction: In patients who are comatose due to head injury, subarachnoid hemorrhage, or cerebrovascular disease, the cerebral arteriovenous difference can be used to estimate cerebral blood flow (CBF) (1). Furthermore, it is common practice to estimate the adequacy of systemic perfusion by monitoring systemic mixed venous oxygen saturation (S_vO_2). We studied the relationship between oxygen saturation in the internal jugular bulb ($S_{jv}O_2$) and CBF during hypothermic, nonpulsatile cardiopulmonary bypass (CPB) in man to determine the applicability of $S_{jv}O_2$ as a monitor of CBF during CPB.

Methods: Following approval by the Institutional Clinical Research Practices Committee, 88 patients undergoing elective cardiac surgery gave informed, written consent. Following premedication with lorazepam 50 mcg/kg po and morphine 0.1 mg/kg im, subjects were given fentanyl 75 mcg/kg, paralyzed with non-depolarizing muscle relaxants, and ventilated with oxygen (F_iO_2 = 1.0) to maintain normocarbia. No additional anesthetic or vasoactive drugs were administered until completion of measurements. CPB was conducted using systemic hypothermia, hemodilution (≈ 27° C and 25%, respectively), membrane oxygenation, arterial line filtration, and blood-free priming solution. CBF was measured using ^{133}Xenon washout. The CBF_{15} calculation, corrected for hypothermia and hemodilution, was used to analyze the clearance curves. During each measurement, mean arterial pressure (MAP), pump flow (Q), nasopharyngeal temperature (NPT), P_aO_2, and hematocrit (Hct) were recorded. Depending upon the duration of stable hypothermia, one or two measurements were performed in each patient. One hundred and twenty-four measurements of CBF and $S_{jv}O_2$ were obtained in 88 patients. The relationship between $S_{jv}O_2$ and CBF was determined by linear regression. All values are expressed as mean ± standard deviation (SD).

Results: The relationship between CBF and $S_{jv}O_2$ was best described by a quadratic equation ($SjVO_2 = 59.71 + 1.65 \cdot CBF - .02 \cdot CBF^2$, $r^2 = 0.3645$). However, as is apparent from inspection of the figure, $S_{jv}O_2$ could not be estimated from knowledge of the CBF. The table compares $PaCO_2$ (mmHg; uncorrected for temperature), nasopharyngeal temperature (NPT; °C), pump flow (Q; L/min/m^2), mean arterial pressure (MAP; mmHg), and hematocrit (Hct; %) at measurements in which $S_{jv}O_2$ (%) was less than 60% with those in which it was greater than or equal to 60%. There are no significant differences in these controlled variables.

TABLE

	$PaCO_2$	Q	NPT	Hct
$S_{jv}O_2$ <60	44.2±7.6	2.0±0.4	27.2±1.4	23.4±3.6
$S_{jv}O_2$ $\geq$60	47.5±9.3	2.0±0.4	27.3±1.1	24.5±3.8

Discussion: Despite the curvilinear relationship between CBF and $S_{jv}O_2$ during CPB, the latter cannot reliably be predicted from the former. Although all values of $S_{jv}O_2$ <60% (≈10% of total values) were found in patients in whom CBF was ≤15 ml/100g/min, values of $S_{jv}O_2$ substantially exceeding 60% frequently occurred at similar levels of flow. Conversely, all CBF measurements >15 ml/100g/min were associated with $S_{jv}O_2$ values greater than 60%. We conclude that assessment of the adequacy of cerebral perfusion during hypothermic CPB requires knowledge of both CBF and $S_{jv}O_2$, particularly at lower levels of CBF. Such levels of CBF occur routinely during hypothermic CPB managed using the α-stat approach, in which P_aCO_2, uncorrected for body temperature, is maintained at 40 mmHg (2).

References:

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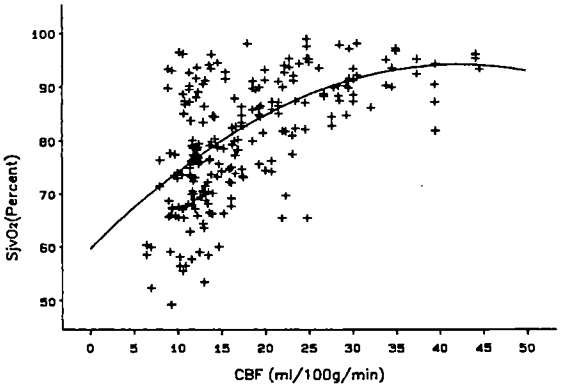

TITLE: SODIUM NITROPRUSSIDE DOES NOT DILATE CEREBRAL RESISTANCE VESSELS DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

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Introduction: In normothermic anesthetized man, cerebral blood flow (CBF) does not change during profound hypotension induced by sodium nitroprusside (SNP) (mean arterial pressure [MAP] = 40 mm Hg) (1). Either SNP directly dilates cerebral resistance vessels, or the vascular bed dilates as MAP declines, i.e., autoregulation persists. Direct vasodilation is suggested by rebound cerebral hyperemia with increased CBF and reduced cerebral vascular resistance (CVR) once MAP is restored to control values after SNP infusion is terminated (1). In order to precisely characterize the influence of SNP on cerebral resistance vessels during hypothermic cardiopulmonary bypass (CPB), we studied patients in whom SNP was administered during concomitant phenylephrine (PHEN) infusion, such that MAP remained unchanged from baseline.

Methods: After approval by our institutional IRB, we obtained informed, written consent from 14 adult patients undergoing elective cardiac surgery. Preoperative exclusion criteria were uncontrolled hypertension, symptomatic cerebrovascular disease (CVD), and asymptomatic extracranial CVD detected by carotid Doppler studies. Following premedication with lorazepam 50 mcg/kg and morphine 0.1mg/kg, patients were anesthetized with fentanyl 75 mcg/kg, paralyzed with pancuronium or metocurine, intubated, and mechanically ventilated with oxygen. Nonpulsatile cardiopulmonary bypass (CPB) was conducted using moderate hypothermia (28°C), hemodilution (24%), membrane oxygenation and arterial line filtration. Group 1 patients (n=8), had alpha-stat blood gas management, whereas group 2 patients (n=6) had pH-stat blood gas management. Baseline measurements of CBF and cerebral arteriovenous oxygen content difference ($A\text{-}VD_{cere}O_2$) were performed after aortic cross-clamping, when nasopharyngeal temperature (NPT) was stable. MAP was then decreased approximately 20% by infusion of SNP, after which PHEN was infused to restore MAP to predrug levels while SNP infusion continued at the same rate; the measurements were then repeated. Central venous pressure (CVP) was maintained close to zero by allowing unrestricted venous drainage to the reservoir of the CPB circuit. CBF was measured bilaterally by ^{133}Xenon washout, following injection of 3-5 mCi into the CPB arterial inflow cannula. $A\text{-}VD_{cere}O_2$ was calculated using arterial and cerebral venous blood samples. The latter were obtained from a 20-gauge retrograde jugular catheter. Cerebral oxygen consumption was estimated as the product of CBF and $A\text{-}VD_{cere}O_2$. Data were analyzed by repeated measures analysis of variance ($p < 0.05$ significant). All values are expressed as mean ± standard deviation (SD).

Results: In both the alpha-stat and pH-stat groups, MAP was unchanged during SNP-PHEN infusion as compared to the baseline values (Table). Additionally, within groups, all controlled variables were identical between measurement intervals (Table). Within groups, CBF decreased from the baseline to the SNP-PHEN measurement interval ($P < 0.001$); whereas $CMRO_2$ remained constant (Table). The CBF decrease was accounted for solely by the effect of elapsed time between measurements (27 ± 8 min, and 27 ± 7 min, respectively). After time correction of the CBF data (2), there was no change in CBF during combined SNP-PHEN infusion (figure, CBF_{est} = time-corrected CBF). Since MAP and CVP were unaltered, CVR (MAP ÷ CBF) remained constant.

Discussion: During hypothermic CPB in fentanyl-anesthetized man, CBF, CVP, and $CMRO_2$ are not altered by SNP infusion. Concomitant PHEN administration permitted distinction of direct effects on the cerebral resistance vessels from that due to cerebral autoregulatory vasodilation. Our data are comparable to those of Michenfelder et al, who reported similar findings in spinal-anesthetized dogs (3). In that study, SNP was administered while normotension was maintained by inflation of a balloon in the descending aorta. No changes were noted in CBF or CVR. In conclusion, SNP does not dilate cerebral resistance vessels during hypothermic CPB in fentanyl-anesthetized man.

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TABLE CONTROLLED VARIABLES
(means ± SD)

	Alpha-Stat		pH-Stat	
Variable	Baseline	SNP-PHEN	Baseline	SNP-PHEN
MAP (mmHg)	71 ± 10	73 ± 9	74 ± 8	71 ± 4
NPT (°C)	27.4 ± 0.6	27.1 ± 0.6	27.0 ± 1.6	26.8 ± 1.5
Hct (%)	24.9 ± 2.9	24.5 ± 3.0	25.8 ± 3.1	25.2 ± 3.3
PaO_2 *	279 ± 57	274 ± 57	311 ± 122	315 ± 104
Q	2.00 ± 0.2	2.00 ± 0.2	2.00 ± 0.3	2.00 ± 0.2
$PaCO_2$ *	41.3 ± 2.7	40.5 ± 1.7	50.0 ± 5.1	50.3 ± 4.9
ET (min)	0	27 ± 8	0	27 ± 7
CBF +	11.7 ± 2.0	10.1 ± 1.4	18.1 ± 5.2	15.3 ± 5.4
CBF_{est} +	-	12.9 ± 2.0	-	19.7 ± 7.6
$CMRO_2$ +	0.4 ± 0.2	0.3 ± 0.2	0.4 ± 0.1	0.4 ± 0.2

MAP = mean arterial pressure; NPT = nasopharyngeal temperature; Hct = hematocrit; Q = pump flow in $l \cdot min^{-1} \cdot m^{-2}$; * = mmHg, uncorrected for body temperature; ET = elapsed time; + = $ml \cdot 100g^{-1} \cdot min^{-1}$

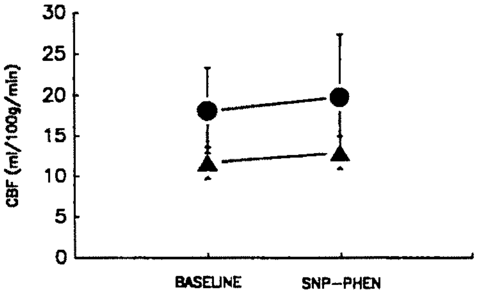

Figure: CBF at baseline, and after SNP-PHEN infusion (time- corrected).

TITLE: **HYPERGLYCEMIA DURING CARDIAC SURGERY: CENTRAL VS PERIPHERAL MECHANISMS**

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Introduction: Recent clinical and experimental evidence suggests that pre-existing hyperglycemia exacerbates ischemic brain injury (1). Despite the considerable neurologic and neuropsychologic morbidity associated with cardiopulmonary bypass (CPB) (2), the contribution of spontaneous hyperglycemia, a frequent occurrence during CPB (3), to those deficits is unknown. No studies determine whether blood glucose (BG) can be tightly controlled during CPB. Optimal control of BG during cardiac surgery requires a knowledge of the specific etiologies of the hyperglycemia. In non-diabetic patients, CPB-induced hyperglycemia is generally attributed to an excess of counter-regulatory (stress) hormones (3). However, the sympathetic nervous system is reportedly suppressed during stable, hypothermic CPB (4,5). To further elucidate the mechanism of CPB-induced hyperglycemia, we studied the relationship among body temperature, BG, and endogenous insulin levels during coronary artery bypass grafting (CABG).

Methods: With the approval of our IRB, 8 adult patients undergoing elective CABG gave informed, written consent for inclusion in the study. None had a history of diabetes mellitus or glucose intolerance. All patients underwent hypothermic non-pulsatile CPB (esophageal temperature ≈ 27°C), using a membrane oxygenator. The pump prime consisted of lactated Ringer's solution and albumin 5%. Following completion of the aortocoronary bypass grafts, systemic rewarming continued until the rectal temperature exceeded 36.5°C, at which time patients were weaned from CPB. Blood samples were withdrawn anaerobically and stored on ice at the following intervals: 1) prior to induction of anesthesia; 2) after induction of anesthesia; 3) after heparinization; 4) 3 min after induction of CPB; 5) after stabilization at an esophageal temperature ≈ 27°C; 6) 30 min after achieving stable hypothermia; 7) during systemic rewarming (blood temperature ≈ 34°C); and 8) following weaning from CPB. Prior to and following CPB, arterial blood samples were withdrawn from a radial arterial catheter. During CPB, arterial samples were aspirated from the arterial inflow tubing of the CPB circuit. To detect any arteriovenous differences in endogenous insulin levels, reflecting net uptake by the CPB circuit, venous blood was withdrawn simultaneously from a central venous catheter at each of the CPB sampling intervals. BG was measured immediately by the glucose oxidase method, and serum insulin levels were later analyzed by radioimmunoassay. For each patient, BG and serum insulin levels at each measurement interval were compared to the control value obtained prior to induction. Results were analyzed by analysis of variance for repeated measures and adjusted using Holm's sequentially rejective multiple testing procedure ($p < 0.05$ significant). All values are expressed as mean ± standard deviation (SD).

Results: BG increased progressively during the course of CABG, from a pre-induction control value of 98 ± 20 mg/dl to a peak value of 250 ± 87 mg/dl during rewarming ($p < 0.001$) (fig). Serum insulin levels decreased from control values during stable hypothermic CPB (16.8 ± 14.8 µU/ml vs 3.9 ± 3.4 µU/ml); due to the large variance, however, this failed to achieve statistical significance. During rewarming, serum insulin levels later rose substantially (187.5 ± 30.8 µU/ml; $p < 0.001$). Following weaning from CPB, BG and serum insulin levels both decreased slightly compared to the peak values, although they remained significantly higher than control values ($p < 0.001$). Arterial and venous serum insulin levels were identical throughout CPB.

Discussion: CPB-induced hyperglycemia appears partially dependent on body temperature. Pancreatic insulin secretion appears to be depressed during hypothermia, since endogenous serum insulin levels fail to rise in response to a progressive increase in BG. Insulin secretion then resumes during systemic rewarming. BG remains elevated, however, consistent with insulin resistance. A similar effect of temperature on epinephrine and norepinephrine secretion during CPB has been described (5). In the rewarming period, hyperglycemia can be attributed in part to the effect of counter-regulatory hormones (5); additionally, hypothermia-induced alterations in peripheral insulin sensitivity may persist, affecting the rate of peripheral glucose uptake. No uptake of endogenously secreted insulin takes place during transit across the CPB circuit. In summary, our data indicate that CPB-induced hyperglycemia results from a combination of hypothermic suppression of pancreatic insulin secretion and insulin resistance.

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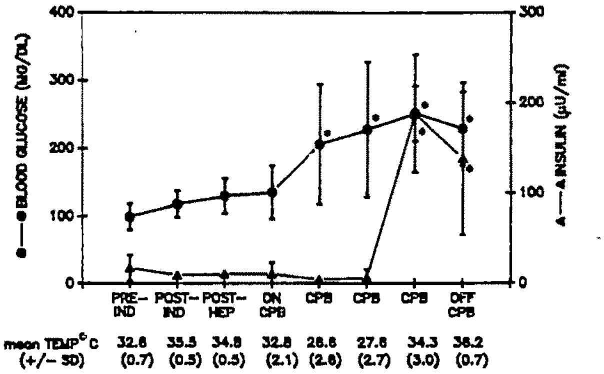

Figure: BG and serum insulin levels at the various sampling intervals. * = $p < 0.001$, compared to baseline (pre-induction).

HYPOXIA DECREASES THE RELEASE OF NEUROPEPTIDE Y FROM DOG PULMONARY ARTERY

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Introduction

Neuropeptide Y (NPY) is a peptide which coexists with norepinephrine (NE) in sympathetic nerve endings in blood vessel walls (1). NPY is released into the synaptic cleft under certain circumstances along with the classical neurotransmitter NE (2). In most blood vessels, NPY potentiates the effect of NE (3). Thus the contraction occurring in blood vessels in response to electrical stimulation (ES), which heretofore was attributed exclusively to the effect of NE, appears to be due to both NE and NPY. Hypoxia is known to increase NE release from dog pulmonary artery, and in the present study we were interested in the effects of hypoxia on NPY release from this tissue.

Methods

The experiments performed in these studies had the approval of the Institutional Animal Care Committee. Adult mongrel dogs of either sex were anesthetized with pentobarbital sodium (30 mg/kg i.v.). The lungs were removed en bloc. Segments of pulmonary artery (2-4 mm OD) were removed from the lower lobes, the parenchyma dissected away, after which the vessels were cut into helical strips. Each strip was suspended in an enclosed superfusion chamber between two platinum wire electrodes in contact with the tissue. ES consisted of rectangular waves (10 V, 0.2 ms, 12, 6, or 1 Hz). The Krebs-Ringer solution used as superfusate was prewarmed to 37°C while being continuously aerated with: (1) 95%-5% CO_2 (PaO_2 = 471 ± 13 mmHg); (2) 5% O_2, 5% CO_2, 90% N_2 (PaO_2 = 50 ± 2 mmHg); or (3) 95% N_2-5% CO_2 (PaO_2 = 20 ± 2 mmHg) (mean ± SE). The gas mixture aerating the superfusate also flowed into the superfusion chamber. The superfusate dripped over the tissue at 2 ml/min. After a 60-min washout seven samples of superfusate were collected at 10-min intervals and passed through Sep-Pak C-18 cartridges. Sample 1 preceded ES, sample 2 was during ES, and samples 3-7 were after cessation of ES. At the end of superfusion the tissue was homogenized, then passed through a Sep-Pak cartridge. Sep-Pak eluates were lyophilized and reconstituted in NPY buffer. A specific radioimmunoassay for NPY using rabbit antibody 58 was used to determine the concentration of NPY (4). HPLC confirmed the presence of authentic NPY in superfusate and tissue homogenate.

Results

Several characteristics of NPY release in response to ES were evident in tissues exposed to high levels of oxygen (PaO_2, 471 mmHg). The release of NPY was frequency-dependent. Although all tissues were stimulated for 10 min, greatest NPY release was measured in tissues stimulated at 12 Hz. NPY in superfusate of tissues stimulated at 6 Hz was less than at 12 Hz but greater than at 1 Hz. The peak NPY level observed in the superfusate always occurred after cessation of ES. Following 12 Hz ES, the peak NPY concentration was in the sample collected in the third post-stimulation time interval (between 30 and 40 min post-ES), and in tissues stimulated at 6 and 1 Hz, peak NPY levels were measured in the second post-ES sample (between 20 and 30 min post-ES). Hypoxia decreased significantly the NPY content of the superfusate during and following ES. The NPY content in superfusate of tissues studied at a PaO_2 of 50 was less than that measured at a PaO_2 of 471 mmHg. Reduction of the PaO_2 further to 20 mmHg caused a further reduction in NPY content in superfusate. Hypoxia, however, did not alter the rate of appearance of NPY in superfusate of tissues stimulated at 12, 6, or 1 Hz as judged by the time following ES at which the peak overflow of NPY was reached.

The NPY remaining in tissues after superfusion and ES was not different in tissues stimulated at 12, 6, or 1 Hz irrespective of the oxygen tension at which the tissues were studied.

Discussion

These studies indicate that the cotransmitter peptide NPY is present in dog pulmonary artery. That NPY is released by the same stimulus that releases NE, suggests that NPY may have a role in initiating or sustaining the contractile response in the pulmonary artery. That NPY may be important in sustaining a NE-initiated contractile response is suggested by the slow onset of release of NPY, the slow attainment of peak levels, and the slow return of peak levels to baseline. Considerable reserve of NPY appears to be present in tissues as ES did not deplete tissue levels of NPY. We initially attempted to relate increased NPY release to the increased contractile response occurring in pulmonary vasculature during hypoxia. While the hypoxia-induced decrease in NPY release measured here does not directly support our hypothesis, additional studies are underway to measure the effectiveness of NPY in potentiating NE-induced contractile responses under hypoxic conditions.

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Supported in part by HL 23217 and GM 41797.

Title: FACTORS AFFECTING CHOICE OF RESIDENCY IN ANESTHESIOLOGY

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Introduction. Considerable time and effort are expended annually by anesthesiology training program directors and faculty evaluating and recruiting trainees. The purpose of this study was to determine which factors resident applicants to our program considered most important in the selection of an anesthesiology training program.

Methods. All residents applying for residency training in anesthesiology at the Mayo Graduate School of Medicine who participated in the 1988 National Resident Matching Program (N.R.M.P.) were mailed questionnaires after the results of the "match" were announced. They were asked to rate the following factors in their selection of a training program in terms of importance: didactic content, geographical area, spousal or family reasons, resident morale, stipend, guaranteed availability of a position, interview experience, research opportunities, case volume, case complexity, availabilty of subspecialty training, recommendation of others, clinical base training offered, institutional reputation, and potential for staff opportunities in the department. Responses of Very Important, Moderately Important, and Unimportant were requested and scored as follows: Very Important = 3, Moderately Important = 2, Unimportant = 1. For each factor, a mean response was calculated. All factors were then ranked using the Mann-Whitney Rank Sum Test. The same survey was distributed to current residents in our department at each level of training and to staff members of the education committee responsible for resident selection. The staff were asked to rate the factors both as they perceived applicants would and as they would if they were now applying for residency training in anesthesiology. The results were compared between N.R.M.P. applicants, current residents and staff using the Spearman Rank Correlation Coefficient.

Results. Response rates were 57/87 (66%) for the total N.R.M.P. applicant group, 14/14 (100%) for the group that "matched" in our program, 17/22 (77%) for the group that ranked high but matched elsewhere, and 26/51 (51%) for the group unmatched by our program due to lower ranking on or exclusion from our match list. Response rates for current residents and staff on the education council were 52/61 (85%) and 10/14 (71%) respectively. The results for 1988 N.R.M.P. applicants to our program are ranked in Tables 1 and 2. There were no statistically significant differences between this group and current residents or staff members on the education committee. Resident morale and program didactic content were the most important factors influencing the choice of training program among N.R.M.P. applicants. Uniformly, guaranteed availability of a position was rated least important.

Discussion. The importance of resident morale on choice of residency program demonstrated in our survey is similar to that reported by Bunch[1] for orthopedic surgical resident applicants. It differs from Sledge et al,[2] who reported the importance of quality of life factors such as geography on choice of residency. Clinical training was consistently viewed as more important than opportunities to pursue research. Though family or spousal factors were rated relatively low on average, it is clear from several comments that these reasons were of great importance to some applicants. Stipend and future staff opportunities were ranked relatively low. It is reassuring that despite allegations of widespread irregularities in the matching process, guaranteed availability of a position was the lowest ranked factor.

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Table 1

MATCHED n=14		MATCHED ELSEWHERE n=17	
Factor	Average#	Factor	Average#
Morale	2.86	Didactic	2.75
Reputation	2.86	Morale	2.69
Didactic	2.79	Subspecialty	2.63
# Cases	2.79	Reputation	2.59
Complexity	2.79	Interview	2.56
Geographical	2.64	Complexity	2.56
Interview	2.64	Recommendation	2.47
Subspecialty	2.57	Geographical	2.44
Clinical Base	2.43	# Cases	2.38
Spouse	2.14	Spouse	2.22
Research	2.07	Clinical Base	2.19
Staff Opportunity	2.00	Research	1.81
Recommendation	1.93	Stipend	1.63
Stipend	1.71	Staff Opportunity	1.56
Guarantee	1.57	Guarantee	1.53

Table 2

UNMATCHED n=26		OVERALL SURVEY RESULTS n=57	
Factor	Average#	Factor	Average#
Morale	2.80	Morale	2.73
Didactic	2.72	Didactic	2.70
Subspecialty	2.62	Complexity	2.59
Complexity	2.60	Subspecialty	2.56
# Cases	2.56	Reputation	2.56
Reputation	2.48	# Cases	2.52
Recommendation	2.34	Interview	2.38
Clinical Base	2.28	Geographical	2.35
Geographical	2.22	Clinical Base	2.25
Interview	2.20	Recommendation	2.24
Spouse	1.92	Spouse	2.03
Stipend	1.60	Research	1.68
Staff Opportunity	1.52	Staff Opportunity	1.62
Research	1.44	Stipend	1.61
Guarantee	1.39	Guarantee	1.46

Title: CONTINUOUS INFUSION EPIDURAL SUFENTANIL FOR POSTOPERATIVE ANALGESIA

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Introduction. Administration of bolus doses of 30,45, or 60 μg epidural sufentanil after cesarean delivery provides effective analgesia having rapid onset, but limited duration.^{1} Subsequent administration of the same doses produces the same analgesic effect, suggesting that bolus administration of epidural sufentanil has no cumulative effect and produces no acute tolerance. We undertook this study to examine the efficacy of sufentanil administration by continuous epidural infusion.

Methods. With approval from our Committee on Human Research, we conducted a prospective, randomized, double-blind study of 48 consenting, healthy women recovering from non-emergent cesarean delivery with epidural anesthesia. Surgical anesthesia was provided by 2% lidocaine with epinephrine (5 μg · ml^{-1}) *via* a lumbar epidural catheter, without supplementary intravenous or epidural opioids. At patients' first complaint of postoperative pain, we injected 10 μg sufentanil (10 ml vol) epidurally, and began a 10-h infusion of sufentanil, diluted in saline, at one of three randomly assigned doses: 2.5, 5 or 10 μg·h^{-1} (each at 10 ml·h^{-1}). Patients assessed pain intensity and subsequent relief using a visual analog scale before and at 3, 5, 7, 10, 15, 30, 45, 60, 90, and 120 min, then hourly, during sufentanil infusion. Simultaneously, an investigator blinded to dose assignment measured blood pressure, heart and respiratory rates, inquired about presence of side effects, and assessed pain intensity and level of sedation using 5-point scales, and intensity of side effects using a 3-point scale. If effective analgesia was not achieved within 15 min of the initial 10-μg dose and the start of infusion, we administered additional doses of 5 μg epidural sufentanil (5-ml vol) every 5 min until patients indicated satsifactory analgesia. No patient received a total bolus dose higher than 30 μg; no patient received bolus doses after 30 min. If patients requested additional analgesia before completion of the 10-h epidural sufentanil infusion, we discontinued the infusion and the study measurements, and administered epidural and/or systemic opioid analgesics to provide relief.

Results. There were sixteen patients in each of the three infusion groups. Patients did not differ in age, height, weight, or total bolus dose given during the first 30 min of epidural sufentanil infusion, nor in vital signs, sedation or incidence or intensity of side effects. The figures illustrate each patient's assessment of pain intensity before and after administration of epidural sufentanil from visual analog scales for each of the three infusion doses. All patients achieved effective analgesia within 30 min of the start of study. However, continuous epidural sufentanil infusion, regardless of dose, failed to sustain effective analgesia for most patients. Despite the differences in infusion doses, the duration of analgesia for the three groups did not differ significantly. Only 1 of 16 patients given 2.5 μg·h^{-1}, 1 of 16 given 5 μg·h^{-1} and 4 of 16 given 10 μg·h^{-1} remained comfortable and did not request additional analgesia for the entire duration of the 10-h infusion.

Discussion. Although epidural administration of low dose sufentanil (10 to 30 μg) reliably produced effective analgesia with rapid onset, continuous epidural sufentanil infusions failed to sustain analgesia. To provide clinically effective, reliable, sustained analgesia after cesarean section, the epidural sufentanil infusion dose must be increased above 10 μg·h^{-1}, the infusion volume must be increased above 10 ml·h, or additional analgesics must be administered.

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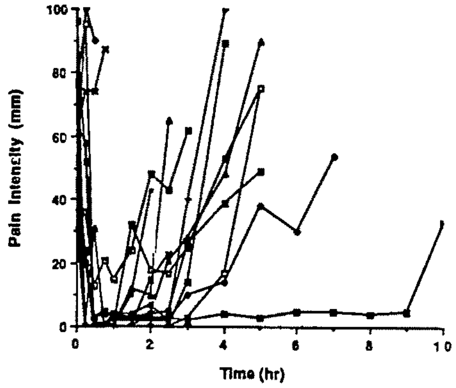
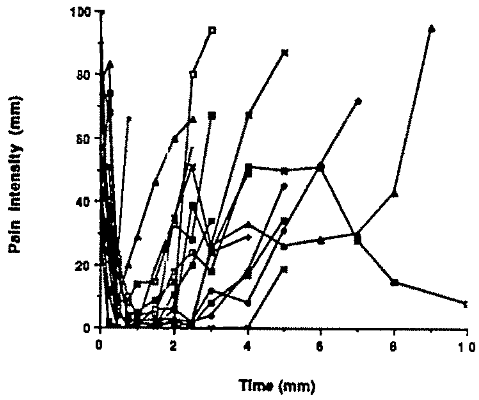
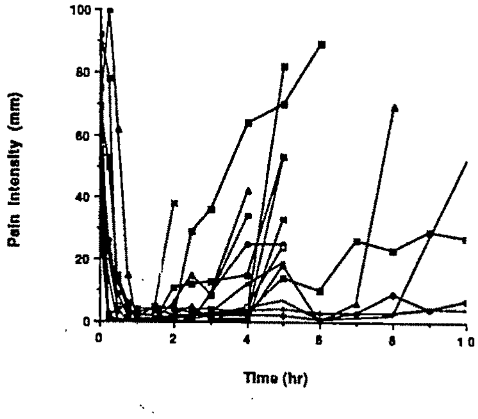
Sufentanil 2.5 μg/hr



Sufentanil 5 μg/hr



Sufentanil 10 μg/hr



Title: HALOTHANE ANESTHESIA IN MICE RESULTS IN A SYMMETRICAL STATE DEPENDENT RETRIEVAL FAILURE

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Introduction: While a lack of awareness and amnesia is an essential part of general anesthesia, the mechanism is not well understood. Exposure to inhalational agents may either interfere with the mechanisms underlying the consolidation of memory or result in a retrieval failure. The purpose of this study was to evaluate the possibility that amnestic effects of halothane on inhibitory avoidance learning is a result of state-dependent retrieval failure.

Methods: The study was approved by the institutional animal research committee. 40 adult Swiss-Webster mice (25-35 gm) were studied and were divided such that half were exposed to halothane and half were exposed to air before training. Mice were anesthetized in a 5L acrylic chamber receiving mixture of 2% halothane with oxygen at a flow of 6L/min for 30 mins. Soda lime was sandwiched between the bottom of chamber and a perforated plate. Recovery time from halothane was measured as the time it took the animal to begin ambulation. Training began 15 min after recovery for anesthetized group. Training took place in a two-compartment shuttle chamber containing both illuminated and darkened compartments. Training was accomplished by placing the mice in the lighted compartment and opening the guillotine door allowing passage to the darkened side, whereupon, the door was lowered and a 0.2mA shock was administered for 1.2 sec. 24 hours later, each group was further subdivided whereupon one group was exposed to halothane in the above-described manner prior to testing, while the other group was exposed to air prior to testing. For testing mice were placed in the shuttle chamber and was allowed passage from the illuminated chamber to the darkened one. Time to cross from the illuminated to the darkened side was measured during the training and testing. Mice failing to cross within 300 secs were assigned a maximum latency score.

Results: Mean recovery time for the anesthetized mice was 8.2 mins. There were no significant differences in the recovery time in any of the groups. After 15 mins, mice were behaviorally indistinguishable from the control animals. The mean testing latencies for the AIR/AIR, HAL/AIR, AIR/HAL and HAL/HAL were 261.9 sec, 88.5 sec, 100.1 sec and 88.5 sec, respectively (see Fig 1). A one-way ANOVA applied to these data indicated that there was a significant difference in test scores among the 4 groups (F(3,36)=6.0; p=.002). Post-hoc comparisons using t tests revealed that the AIR/HAL group had significantly shorter test latencies than the AIR/AIR group (t(18)=3.72; p=.001) and that the HAL/HAL group exhibited significantly longer latencies than the HAL/AIR group (t(18)=2.15; p=.04). These data show that animals trained following air exposure become amnestic if they are anesthetized with halothane before testing, and that mice that would ordinarily be amnestic after being trained following halothane have a restoration of memory if they are re-exposed to halothane before testing.

Discussion: These findings provide strong evidence that halothane anesthesia results in a symmetrical state-dependent retrieval failure in mice. Other drugs which induce dissociative state-dependent learning include ethanol, barbiturates, benzodiazepines and THC. Exposure to halothane may produce alterations in neural excitability accompanied by highly discriminable internal stimuli. The altered central and peripheral stimulus conditions would provide a unique context within which the avoidance response is learned. When animals are tested at a time when the brain has returned to its normal mode of functioning, memory may fail because the stimulus conditions at retrieval are different from those which existed at time of encoding.[1] Prior studies have aimed to distinguish between memory and awareness by attempting to retrieve post-operatively information presented to anesthetized patients. One study showed non-verbal response to suggestions made intraoperatively undergoing inhalational anesthesia accompanied by complete amnesia.[2] A second study failed to show that patients could recognize verbal material which was presented intraoperatively while anesthetized.[3] This study demonstrates strong evidence for state-dependent retrieval failure with halothane anesthesia.

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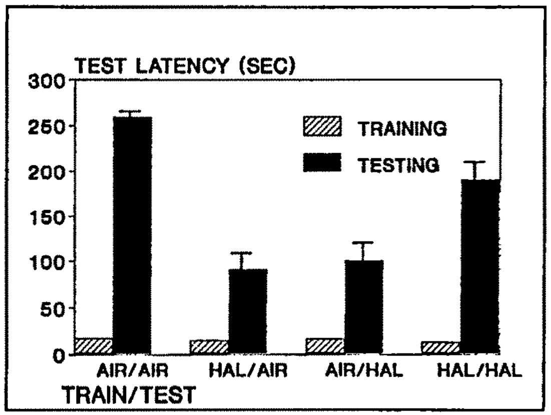

Figure 1. Test Latencies When Mice Are Exposed To Air Or Halothane Prior To Training As Well As Testing.

Title: RETROGRADE AND ANTEROGRADE AMNESIA IN MICE UNDERGOING HALOTHANE ANESTHESIA

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Introduction: It is known that inhalation anesthetics affect memory processes. However, the basis of these memory disturbances are not well understood. The aim of this study was to assess the amnestic properties of halothane using an animal model.

Methods: The study was approved by the institution's animal research committee. Adult male Swiss-Webster mice (25-35 g) were studied. A two-compartment shuttle chamber consisting of an illuminated and a dark compartment was used for training and testing. Each mouse was placed into the illuminated chamber and the door was opened, allowing the animal passage to the dark compartment where a 0.2 mA shock was administered for 1.2 sec. In Experiment 1, the mouse was placed in 5L acrylic chamber receiving a mixture of 2% halothane in oxygen with a flow of 6L/min. Soda lime was sandwiched between the bottom of the chamber and a perforated plate. 4 groups of mice (N=10/group) were exposed to halothane for 15, 30 or 60 min or air for 30 min (control group). Memory retention was tested 24 hr later by placing the animal in the illuminated compartment and opening the door to allow passage to the dark compartment. Time to cross over was measured for training (before halothane exposure) and testing (24 hrs after halothane exposure) with a maximum allowed testing latency of 300 sec. In Experiment 2, 20 mice were anesthetized for 30 min as described above and then trained 15 mins after recovery from anesthesia (defined by initiation of ambulation). 2 groups (n=10/group) were tested 10 min or 24 hr after training. A control group of mice (not exposed to halothane) was trained and tested at 10 min and 24 hrs (n=10/group).

Results: In Experiment 1 where mice were first trained and then exposed to the anesthetic, the respective test latencies for halothane of 15, 30 or 60 min were 243.2, 200.3, 221.9 sec and control was 261.8 sec (Fig 1). A one-way ANOVA (F=.89) showed no significant differences. In Experiment 2 where halothane was administered prior to training, mean recovery time from was 8.5±2.5 min. After 15 min, mice were behaviorally indistinguishable from controls. Initial training latencies for the halothane and air groups were 20.1 and 18.3 sec, respectively. When animals were tested 10 min after training, halothane and control groups had latencies of 83.9 and 105.7 sec, respectively. When animals were tested 24 hr after training, halothane and control group latencies were 88.5 and 261.9 sec, respectively. A two-way ANOVA indicated that there was a significant difference in retention between the 2 groups (F(1,36)=9.34; p=.004),with a significant overall effect of time of testing (F(1,36)=6.34; p=.015), as well as a significant interaction between treatment group and test interval (F(1,36)=5.64; p=.021).

Discussion: Our data indicate that halothane anesthesia in mice can induce anterograde amnesia but not retrograde amnesia for inhibitory passive avoidance learning. Futher, we observed slow development of learning when tested at 10 minutes. This phenomenon of slow learning has been demonstrated by other authors and may involve changes in the cholinergic synapses(1). Retrograde amnesia after halothane has been observed in other animal models. Chicks exposed to halothane had decreased imprinting response(2). Since halothane did not cause retrograde amnesia in our study, avoidance learning may involve different neural mechanisms than does imprinting.

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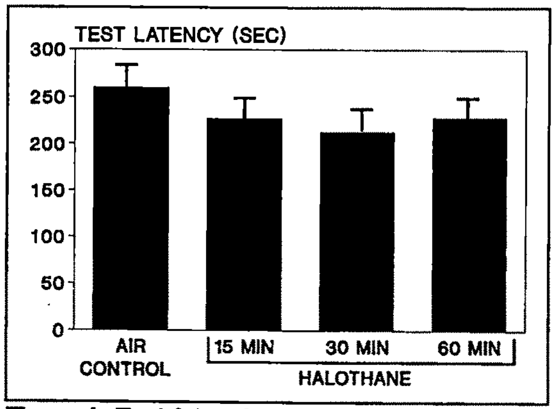

Figure 1. Test latencies following exposeure to air or halothane after training.

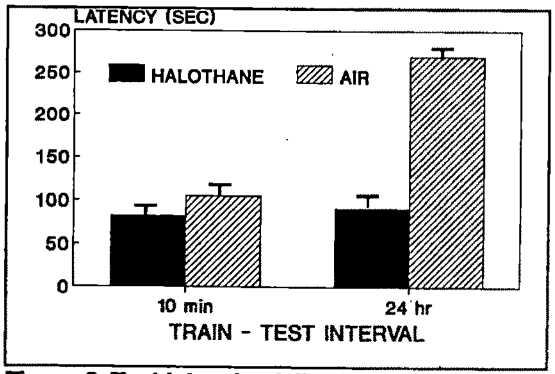

Figure 2. Test latencies following exposure to air or halothane before training.

TITLE:

COMBINED USE OF FENTANYL AND ALFENTANIL IN LONGER SURGICAL PROCEDURES

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Introduction: Alfentanil is a rapidly acting fentanyl derivative with a short duration of action as a result of its rapid redistribution and elimination. For longer surgical procedures, several continuous infusion techniques have been described.[1-3] The purpose of this study was to determine the clinical feasibility of the combined use of fentanyl with alfentanil in patients undergoing longer surgical procedures. Cardiovascular stability, recovery time, patient acceptance, and post-operative side effects were studied.

Methods: 14 ASA 1 or 2 patients with ages ranging from 16 to 60 years were studied. The protocol was approved by the NYU Medical Center Institutional Board of Research Associates. All patients were premedicated with midazolam .07 mg/kg IM. Monitoring included EKG, Dinamap, pulse oximetry, and twitch monitor. All patients received droperidol 0.1 mg/kg IV. After preoxygenation, patients were induced with fentanyl 6-8 mcg/kg. IV bolus followed by thiopental 2-4 mg/kg. After loss of consciousness, vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg for intubation and then ventilated with a 2:1 nitrous oxide:oxygen mixture. Alfentanil 10 mcg/kg IV bolus was given for a 15% increase in systolic blood pressure or heart rate from the preinduction valve. Neuromuscular blockade was assessed with twitch monitoring of the ulnar nerve. Reversal was accomplished with prostigmine .06 mg/kg and glycopyrvolete 0.1 mg/kg. Time to achieve nitrous oxide, recovery time was determined with spontaneous breathing at 0.1 L kg^{-1} min^{-1} and the ability to maintain a 5 second head lift after discontinuing nitrous oxide was measured. Respiratory rate and analgesia were observed for an additional hour. Patients were interview 24 hours later.

Results: 8 patients were female, 6 male with ages 35.7±14 year (meant SD) and weight 66.2±11.5 Kg. The patients studied underwent a variety of surgical procedures including gynecology, orthopedics, plastic surgery, general surgery and urology. Range of duration of procedures was from 45 minutes to 240 minutes with a mean of 102±47 minutes. After intubation the rise in systolic blood pressure and heart rate was 2±4 mm and 2±3 beats per minute respectively. 14 patients (100%), received alfentanil to supplement anesthetic maintenance as determined by changes in blood pressure, heart rate, or patient response to surgical stimulation. Nine patients (65%) required alfentanil immediately after skin incision. Time interval between supplementary alfentanil bolus and induction was 15±18 minutes. A second bolus of alfentanil was given in 13 patients (93%) with a time interval between first and second bolus of 27±25 minutes. Eleven patients (79%) required additional boluses of alfentanil. Recovery time after reversal of muscle relaxants and discontinuation of nitrous oxide was 6±2 minutes. Mean recovery room respiratory rate was 15±3 breaths per minute. Post-op analgesia was judged adequate in all the patient in the recovery room for the next hour. All patients were satisfied with their anesthetic and denied recall of any intraoperative events when seen post-operatively.

Discussion: The combination of fentanyl and alfentanil appears to be an effective nitrous narcotic anesthetic technique patients were stable hemodynamically .during induction and throughout the surgical procedures ranging from 45-240 minutes. Recovery was prompt and post-op analgesia have judged adequate. Alfentanil levels rapidly decline after a single infection while a single dose of Fentanyl 10 mcg/mg may maintain levels 1-2 mg/ml for 2 or more hrs and produce respiratory depression.[4] The strategy of this technique was to initiate narcosis with a smaller dose of longer lasting fentanyl (6-8 mcg/mg), and then supplement with intermittent boluses of alfentanil and thereby reduce the possibility of postoperative respiratory depression. In conclusion, the combination of fentanyl and alfentanil appears to be a safe and effective technique for nitrous narcotic anesthesia.

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PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING BY HALOPERIDOL OR DROPERIDOL

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INTRODUCTION: Nausea and vomiting following anesthesia and surgery is recognized as a major contributor to patient distress in the early postoperative period and is estimated by various authors to occur in 19 to 55 percent of patients (1). Droperidol is recognized as useful in reducing the incidence of postoperative nausea and vomiting but can lead to sedation which may delay discharge of the ambulatory surgical patient. Metoclopramide has been shown to have limited utility as a postoperative antiemetic (2). Haloperidol has been shown to be an effective antiemetic in patients receiving chemotherapy and in postoperative patients (3, 4). This double blind study was undertaken to compare the incidence of nausea and vomiting in patients having a standardized anesthetic and similar surgical procedures after pretreatment with droperidol, haloperidol, metoclopramide or saline as a control.

METHODS: Following a protocol approved by our institution's Human Investigation Committee 48 female patients between the ages of 20 and 40 scheduled for laparoscopy for bilateral tubal ligation were enrolled as subjects for study. On the day of surgery each patient was randomly assigned to one of four treatment groups by drawing lots. The treatment groups were:

A metoclopramide --.15 mg/Kg in normal saline q.s. 4.0 ml.
B droperidol--10 ug/Kg in normal saline q.s. 4.0 ml.
C haloperidol--7 ug/Kg in normal saline q.s. 4.0 ml.
D normal saline--4.0 ml.

The drugs were prepared and labeled with the patient's name and delivered to the individual conducting the anesthetics shortly before anesthetic induction. Each patient was anesthetized using a common anesthetic technique consisting of 1-2 ug/Kg fentanyl and 2-3 mg of curare prior to induction. Anesthesia was induced with 3-4 mg/Kg thiopental followed by 1-1.5 mg/Kg succinyl choline to facilitate tracheal intubation. Anesthesia was maintained with 50-70 percent nitrous oxide in oxygen and isoflurane as needed. Intraoperative muscle relaxation was obtained with atracurium as needed and was monitored with a peripheral nerve stimulator. Shortly after the induction of anesthesia the treatment medication (i.e. A, B, C or D) was administered intravenously.

Postoperatively patients received routine post anesthesia care and monitoring. The post anesthesia nursing staff recorded any episodes of vomiting and inquired about feelings of nausea. Every patient received two scores, one for nausea and one for vomiting, during each of four thirty minute intervals according to the following scale:

0 No nausea or vomiting
1 Mild to moderate nausea or 1 or 2 episodes of retching or vomiting
2 Severe nausea or more than 2 episodes of retching or vomiting

When patients were ready for discharge they departed and were removed from the study, thus fewer are patients included in the later intervals (N {0-30'} = 48; N {30-60'} = 47; N {60-90'} = 39; N {90-120'} = 18). The individual nausea and vomiting scores in the four treatment groups were compared within each of the four time intervals using an analysis based on ranks (Kruskal-Wallis). When the Kruskal-Wallis test statistic (H) exceeded the critical value for $P=<.05$ we concluded that at least one treatment group had less nausea or vomiting than others in that time interval. We then performed pairwise comparisons using Mann-Whitney rank sum tests (with a Bonferroni adjustment) to identify the significantly different pairs ($P = <.05$) at each interval.

RESULTS: Examination of the distribution of the nausea and vomiting scores in the control groups revealed the greatest incidence of both nausea and vomiting to be during the 30-60 min. and 60-90 min. intervals in the PACU. Throughout this study the scores for vomiting were less than scores for nausea. Nausea and vomiting scores in all four intervals were highest in the control (SAL) and metoclopramide (MET) groups and lowest in the droperidol (DRO) and haloperidol (HAL) treated groups.

TOTAL OF INDIVIDUAL SCORES

	NAUSEA				VOMITING			
INTERV\Rx	**MET**	**DRO**	**HAL**	**SAL**	**MET**	**DRO**	**HAL**	**SAL**
0-30'	3	1	3	5	1	0	2	2
30-60'	6	2	3	9	5	0	3	4
60-90'	5	2	2	9	4	1	2	4
90-120'	4	0	2	6	4	0	2	2

The differences between the droperidol and haloperidol treated groups and the control groups were significant during the 60-90 min. interval (Nausea: $P < .025$; Vomiting $P < .012$). None of the patients in this study sustained any adverse effects from any of the drugs used.

DISCUSSION: This study shows that nausea and vomiting are not conspicuous early in recovery from general anesthesia but after thirty minutes become more prominent. This may correspond to increasing patient movement during a period of altered reflexes involving medullary centers mediating emesis. We conclude that metoclopramide is ineffective in preventing postoperative nausea or vomiting. This study demonstrates that i.v. haloperidol, like droperidol, is effective in the prophylaxis of postoperative nausea and vomiting. In the dose used it caused little sedation and any sedative effect was of shorter duration than that following droperidol. Further study will be needed to define the effect of varying the time of administration and the dose of haloperidol.

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Title: FENTANYL AS AN EPIDURAL INTRAVASCULAR TEST DOSE IN OBSTETRICS

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Introduction: Recognized intravascular placement or migration of an epidural catheter occurs in 5.2% of obstetrical anesthesia cases. There are various precautions recommended to avoid intravascular injections of local anesthetics, however, at the present time, there exists no universally accepted method to identify an intravascular catheter in a patient who is in labor.

Fentanyl is a popular analgesic used either intravenously or epidurally throughout labor. Common side-effects produced by fentanyl include dizziness and drowsiness. These side-effects are directly related to the concentrations of fentanyl in the blood. Thus, although they may be produced with either intravascular or epidural fentanyl, the side-effects following intravascular administration should theoretically occur more rapidly, and appear to be relatively more pronounced. The purpose of this study was to determine whether or not the difference would allow reliable detection of an accidental intravascular injection.

Methods: After institutional approval, 80 administrations of fentanyl were made in women in active labor. The patients were divided into four groups. Groups I & II received intravenous injections, while groups III & IV received epidural injections. Using a randomly assigned double-blinded technique, each patient received 2 injections separated by a 3 minute observation period. Groups I & III were given 2 cc of normal saline (NS), followed by 2 cc of fentanyl (100ug), while in groups II & IV, the order of solution administration was reversed. Before receiving any administrations, a baseline level of dizziness and drowsiness was determined. Then, the subjects were assessed at one minute intervals for any subjective change in sensorium for the three minutes following each solution. In the epidural fentanyl groups (III & IV), 3 cc of 0.25% bupivacaine without epinephrine was given through the epidural catheter, 3 minutes before any other solutions, as a subarachnoid test dose.

Results: All patients denied any baseline dizziness or drowsiness.

	Dizziness/Drowsiness	
Intravenous (IV)	Injection #1 Minutes 1-3	Injection #2 Minutes 4-6
Group I	IV NS 0/18	IV Fent 18/18
Group II	IV Fent 22/22	IV NS 21/22
Epidural (E)		
Group III	E NS 0/18	E Fent 1/18
Group IV	E Fent 1/22	E NS 1/22*

(*) Same patient which reported (+) response to E-Fent.

Discussion: When compared with epidural fentanyl, the changes resulting from IV fentanyl appear to occur in a remarkably more consistent fashion. Indeed, all subjects who received IV fentanyl reported unmistakable changes in sensorium. There were no false negatives (misses). Therefore, fentanyl appears to be extremely sensitive as an intravenous test with a negative result having a predictive value approaching 100%. Furthermore, there were only 2/40 false positives (false alarms) following epidural fentanyl. Thus, fentanyl also appears to be an extremely specific marker of IV administration with a positive result having a predictive value of 95%.

In addition to being highly sensitive and specific, fentanyl demonstrated several other desirable features of a test dose. Unlike other agents used as intravascular markers, fentanyl is an effective analgesic. It is routinely used intravenously, in 100ug doses in our laboring patients without any apparent untoward effects on respiration. When administered epidurally, its maternal neonatal safety is well documented.[2] And, unlike some other test dose agents, it does not have any known adverse effects on uterine blood flow or uterine contractility.[3] Although the side-effects of fentanyl were pronounced, they did not appear to be extremely unpleasant. It appears to yield rapid results, usually within the first minute after administration and does not require any complex monitoring. Beyond its simplicity, the effects of IV fentanyl appear to be distinct from the usual cyclical changes that occur throughout labor. Furthermore, the effects of IV fentanyl appear to last for at least several minutes and therefore, are not as likely to be missed. Indeed, in group II, 21/22 patients indicated that the effects of IV fentanyl persisted throughout the entire 6 minute period of observation. However, due to the relatively short clinical duration of fentanyl, it should be effective, when used repeatedly with each top-off throughout labor.

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TITLE: **AGE DOES NOT AFFECT CEREBRAL AUTOREGULATION DURING HYPOTHERMIC CARDIOPULMONARY BYPASS IN MAN**

AUTHORS: RC Roy, MD, PhD, AT Rogers, MBChB, DS Prough, MD, DA Stump, PhD, C Taylor, MAS, T Daniels, BS
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Introduction: Age has been implicated as one of many risk factors in the genesis of neurologic injury associated with coronary artery bypass grafting (CABG) (1). Although clinical studies have failed to identify an association between cerebral perfusion pressure during cardiopulmonary bypass (CPB) and subsequent brain injury (1,2), recommendations are often made that mean arterial pressure (MAP) be higher during CPB in the elderly (age > 70 years) (1,3). These recommendations are based on the presumption that autoregulation may be abnormal in a group of patients who have a high incidence of asymptomatic cerebrovascular disease (CVD). We studied cerebral blood flow (CBF) in a large group of patients with a wide range of ages undergoing CPB and examined the influence of age on cerebral autoregulation.

Methods: One hundred and fifty-five patients gave informed, written consent to participate in the study after approval by the Clinical Research Practices Committee. All patients were free of uncontrolled hypertension and symptomatic CVD. Following premedication with oral lorazepam and im morphine, patients were anesthetized with fentanyl 75 mcg/kg, paralyzed with pancuronium and/or metocurine, intubated, and mechanically ventilated with oxygen. Other than heparin, no other anesthetic or vasoactive drugs were administered prior to completion of measurements. Non-pulsatile CPB was conducted using moderate hypothermia and hemodilution with a membrane oxygenator and arterial line filter. After aortic cross-clamping, once nasopharyngeal temperature (NPT) was stable, regional CBF (16 detectors) was measured once in each patient by clearance of ^{133}Xenon (3-5 mCi) injected via the aortic inflow cannula. Arterial blood gases were managed according to the alpha-stat method ($P_aCO_2 < 50$ mm Hg, uncorrected for temperature). For purposes of statistical analysis, patients were divided into three age groups: group 1 (< 57 years, n = 56), group 2 (57-66 years, n = 51), and group 3 (> 66 years, n = 53). Within each group, linear regression analysis was used to correlate CBF and MAP; $p < 0.05$ was considered significant. All values are expressed as mean ± standard deviation (SD).

Results: NPT, hematocrit (Hct), P_aO_2, pump flow (Q), and P_aCO_2 were similar among groups (table). CBF was independent of MAP in each age group across a comparable range of MAP values. The r^2 values were 0.013, 0.016, and 0.001 for groups 1, 2, and 3, respectively (figure). There was no significant difference among the intercepts or slopes of the three regression lines.

Discussion: These data confirm previous observations regarding the absence of a significant correlation between MAP and CBF during alpha-stat CPB management, i.e., cerebral autoregulation remains intact (4). Additionally, this study in a large group of patients agrees with the conclusions of Brusino et al (5), that the relationship between CBF and MAP is unaffected by age. Accordingly, recommendations for higher MAP (> 70 mm Hg) in elderly patients may be unnecessary. Further study is required before these conclusions can be extrapolated to cardiac surgical patients with symptomatic CVD.

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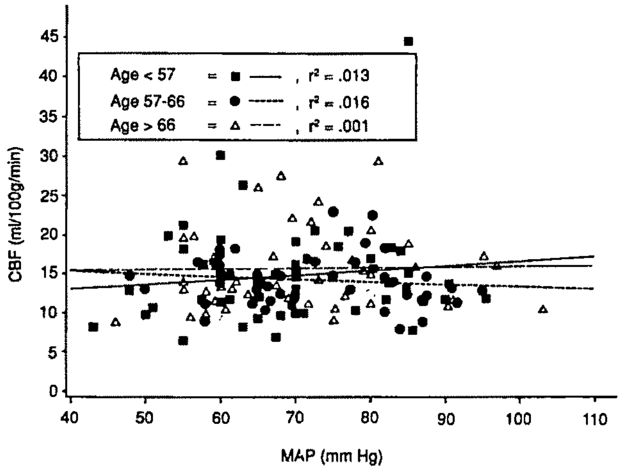
TABLE

Variable	Group 1 Age <56	Group 2 Age 57-66	Group 3 Age >66
Age	48.5 ± 7.2	60.8 ± 3.1	71.2 ± 3.6
MAP (mmHg)	69.2 ± 12.4	72.1 ± 11.7	70.4 ± 12.3
NPT (°C)	27.3 ± 1.4	27.3 ± 1.1	27.1 ± 1.2
Hct (%)	24.5 ± 4.0	23.8 ± 3.3	22.8 ± 3.9
PaO_2 (mmHg)	269 ± 74	269 ± 80	250 ± 72
Q (l•min^{-1}•m^{-2})*	2.0 ± 0.3	1.9 ± 0.4	2.0 ± 0.4
$PaCO_2$ (mmHg)*	41.2 ± 4.0	42.5 ± 4.0	40.8 ± 4.1



Title: NONINVASIVE ESTIMATION OF CARDIAC OUTPUT FOLLOWING CARDIAC SURGERY

Authors: Rob J. Roy, D.Eng.Sc., M.D.* and John M. Capek, Ph.D.**

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Introduction. This paper describes the use of a cardiac output estimation technique [1] based on a differential form of the CO_2 Fick equation on post-cardiac surgery patients. The use of the Fick equation in a differential form eliminates the need to estimate mixed venous pCO_2 and reduces the sensitivity of the algorithm to elevated alveolar deadspace fractions and other $\dot{V}/\dot{Q}$ maldistributions which affect the arterial to end-tidal pCO_2 gradient.

A sudden onset of partial rebreathing causes a change in CO_2 elimination ($\dot{V}$) and arterial CO_2 content (C_a). Under the assumptions that cardiac output ($\dot{Q}$) and mixed venous CO_2 content ($C_{\bar{v}}$) remain constant, the Fick equation can be evaluated before (1) and at the conclusion (2) of the partial rebreathing period and solved for Q. The linear shape of the CO_2 dissociation curve allows the small change in C_a to be approximated from the change in arterial pCO_2 (P_{aCO2}) multiplied by the slope (S) of the dissociation curve. Noninvasive estimates of P_{aCO2} can be obtained from measurements of end-tidal pCO_2 (P_{ETCO2}) provided they are corrected by a multiplicative factor (K) which can be evaluated using simultaneous determinations of the arterial and end-tidal pCO_2.

$$\dot{Q} = \frac{-\Delta\dot{V}}{SK\Delta P_{ET}}$$

where

$$\Delta P_{ET} = P_{ET}(2) - P_{ET}(1) \qquad (2)$$

$$\Delta\dot{V} = \dot{V}(2) - \dot{V}(1). \qquad (3)$$

A sensitivity analysis of equation (1) reveals that the cardiac output estimate is relatively insensitive to errors in the determination of K, allowing an approximation (K=1.11) to be used in the absence of an arterial blood sample.

Methods A Siemens 900C Servo-ventilator was used with a 930 CO_2 Analyzer to provide instantaneous measurements of airway flow and airway CO_2. Analog outputs from both the ventilator and CO_2 analyzer were processed on an IBM PC-XT. Two valves were activated for 30 seconds, every five minutes, temporarily introducing 150 ml of airway deadspace into the ventilation circuit.

Breath-by-breath CO_2 elimination was calculated by integrating the product of airway flow and airway CO_2. End-tidal pCO_2 was determined as the maximum CO_2 value for each breath. $\dot{V}(1)$ and $P_{ET}(1)$ were calculated at the conclusion of each normal ventilation period as the average of the values measured over the past one minute. $\dot{V}(2)$ and $P_{ET}(2)$ were calculated as the average values measured during the partial rebreathing period, excluding the first breath.

Twenty-two male and eight female patients, ages 52 through 77, were monitored for one hour, between 90 and 300 minutes following cardiac surgery in the cardiopulmonary surgery recovery room. The protocol was approved by the AMC Human Research Committee. Patients were ventilated using Synchronous Intermittant Mandatory Ventilation (SIMV) at settings determined by respiratory care. Thermodilution measurements of cardiac output were made in triplicate every 15 minutes. Vital signs, pulmonary artery, and pulmonary capillary wedge pressures were simultaneously recorded.

Results. A sample of the data obtained from a typical patient is shown in Figure 1. The sharp increases in end-tidal pCO_2 and reductions in CO_2 elimination are a direct result of the partial rebreathing periods. The cardiac output estimates (0) obtained from equation (1) are shown compared to the thermodilution (X) values.

Comparison of the noninvasive cardiac output estimates ($\dot{Q}_{PRB}$) with thermodilution measurements ($\dot{Q}_{TD}$) for all 30 patients yielded a regression line $Q_{PRB}=1.04Q_{TD}-.31$ with a correlation coefficient of .83. There was no systematic error over a wide range of cardiac outputs (3.3-7.5 l/min), intrapulmonary shunts (3.2-24.2%), and alveolar deadspace fractions (0.0-27.8%).

Discussion. This paper describes a technique for estimating cardiac output based on the differences in P_{ET} and $\dot{V}$ measured during 30 seconds of partial rebreathing. The algorithm used to estimate $\dot{Q}$ is different from other noninvasive applications of the CO_2 Fick equation in that the need to estimate mixed venous pCO_2 has been eliminated. The technique only requires the measurement of airway flow and airway CO_2 and can be implemented with virtually any commercially available ventilator.

This work was supported in part by Siemens Ventilator Systems and NIH GM-15426.

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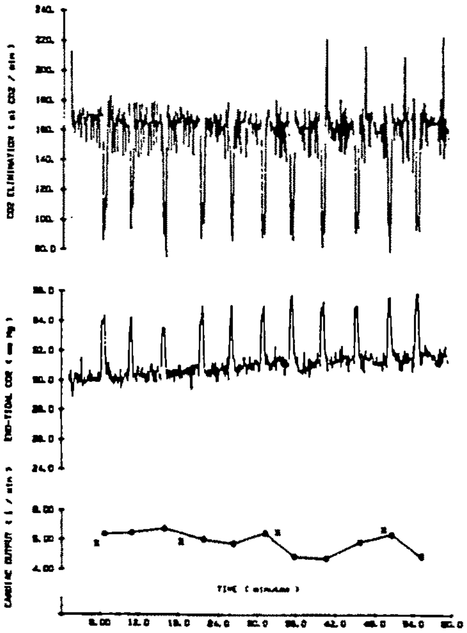

TITLE: ATRACURIUM INFUSION VERSUS PANCURONIUM INTERMITTENT BOLUS: TITRATION TO THE THERAPEUTIC WINDOW AND SUBSEQUENT RECOVERY

AUTHORS: S.M. Rupp, M.D. and C.A. Stephenson, R.N.

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Introduction: Infusion of nondepolarizing muscle relaxant (NDMR) has recently drawn considerable interest,[1-3] particularly with the introduction of the newer short and intermediate acting NDMR's. In this study we compared infusion of atracurium (atra) to a more traditional intermittent pancuronium (panc) bolus technique in their ability to keep muscle relaxation in the therapeutic window (adequate relaxation yet antagonizable block), work intensiveness, and ease of antagonism of neuromuscular blockade at the end of surgery. The drugs used for each technique were chosen because they were felt to represent the prototype for that technique.

Methods: Institutional Human Research Committee approval was obtained. 41 healthy adult ASA I or II patients undergoing otological surgery gave informed consent to participate and were randomized to receive either atra or panc as the relaxant. Patients were sedated with midazolam 1 mg and fentanyl 50 ugm. Anesthesia was induced with thiopental 2-4 mg/kg iv and then maintained with isoflurane (0.65% end-tidal), 60% nitrous oxide and increments of fentanyl to keep the end-tidal concentration of isoflurane constant. Ventilation was maintained constant ($ETpCO2=30mmHg$). Neuromuscular function was monitored via force-of-thumb adduction (FT-10 force transducer) in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist. After a stable baseline was obtained, a defasciculating dose of relaxant (atra 0.05 mg/kg or panc 0.01 mg/kg) was administered. 3 min later succinylcholine 1.25 mg/kg was given and after abolition of twitch, the trachea intubated. At 25% recovery of the first twitch (T1) a 'set-up' dose of atra 0.3 mg/kg or panc 0.04 mg/kg was administered. Subsequent dosing was as follows: for atra an infusion 7.5 ug/kg/min was begun when T1 started to recover and was adjusted up or down to keep T1 between 1 and 15% of control T1 (Tc). For panc, boluses of 0.015 mg/kg were given whenever T1 recovered to 15% of Tc. Ability to keep T1 in the therapeutic window (%T1 in Tx window) was calculated as the %time T1 was 1-15% Tc between the initial 'set-up' dose and the last surgical stitch. Work intensiveness was compared between groups by comparing the number of top-up boluses for panc and number of infusion adjustments for atra. After the last surgical stitch, T1 was allowed to recover to 15% and then neostigmine 0.04 mg/kg with glycopyrrolate 0.01 mg/kg was administered. If after 10 min the T4/T1 ratio was < 0.6 or not increasing greater than 2%/min for 3 minutes, an additional dose of neostigmine 0.04 mg/kg with glycopyrrolate 0.01 mg/kg was administered. Adequacy and speed of restoration of neuromuscular function was compared between groups by: (1) comparing the time from the last stitch to administration of antagonist (TLS-REV); (2) time from REV to a T4/T1 ratio of 0.7 (REV-T470%); (3) number of second doses of antagonist required. Values were compared using unpaired t-test except need for additional reversal which was compared using the Fisher exact test. $P < 0.05$ was considered significant.

Results:

	Atra	Panc	P
duration of surgery	155 (64)	145 (56)	0.59
Time T1=0% after bolus	25 (9)	22 (14)	0.48
%T1 in Tx window	78 (14)	54 (19)	.0001*
#adjust/#top-ups	3.9 (2)	3.6 (2)	0.72
time TLS-REV	7 (4)	9 (7)	0.29
time REV-T470%	8.6 (3.5)	13.4 (7)	0.01*
Additional Reversal	1	7	0.02*

All times are minutes. Values are mean (S.D.)

Discussion: Atracurium infusion can keep T1 within the therapeutic window significantly more than pancuronium intermittent bolus. This is despite the fact that the time T1=0% after the 'set-up' bolus of relaxant was not different between groups. We intentionally gave a less potent panc 'set-up' dose (potency ratio 1 panc/7.5 atra) and small panc 'top-up' doses to minimize the amount of time that T1=0% (and hence out of the Tx window) in that group. Had equipotent 'set-up' doses been given (potency ratio 1 panc/3-4 atra)[3] the difference in %T1 in Tx window would probably have been even greater. The lack of difference in # adjustments atra infusion vs. # top-ups panc suggests that the two techniques have similar work intensiveness (excluding the initial atracurium infusion set-up). The speedier recovery of T4/T1 and less need for additional reversal coupled with the larger %T1 in Tx window in the atracurium group suggests that this technique allows more control of neuromuscular blockade.

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TITLE: FLUMAZENIL VERSUS PLACEBO IN ANTAGONISM OF MIDAZOLAM-BASED GENERAL ANESTHESIA FOR OUTPATIENT SURGERY

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Introduction: Flumazenil (RO 15-1788) is a competitive benzodiazepine receptor competitive antagonist undergoing clinical trials.[1-3] Without a drug of this type, the use of benzodiazepines for induction and maintenance of general anesthesia for short procedures has been limited due to the duration of post-operative sedation (which can occasionally be markedly prolonged). Accordingly, we compared the effects of flumazenil versus placebo in their effects on recovery from general anesthesia induced by midazolam for short outpatient procedures. This study represents the results from one center in a multicenter study.

Methods: Institutional Human Research Committee approval was obtained. Thirty healthy adult ASA I or II outpatients undergoing short gynecologic or urologic procedures gave informed consent to participate. The design was double-blind. Anesthesia was induced and maintained with midazolam 0.1 mg/kg, fentanyl 1.3 ugm/kg iv and 60-70% nitrous oxide with isoflurane 0.2-0.4% inspired via face mask. Ventilation was spontaneous. Additional midazolam 0.015-0.03 mg/kg iv was administered throughout the case as needed to maintain adequate levels of anesthesia. Upon arrival in the recovery room (PACU), vital signs and an initial assessment of the patient's level of sedation (see table 1) were taken by an independent trained observer. Patients had to receive a score of 3 or less upon arrival in the PACU to be entered in the study. Table 1:

Responsiveness	Speech	Expression	Eyes	Score
Responds readily	Normal	Normal	Clear, no ptosis	5
Lethargic to name called	Mildly Slowed	Mild Relaxation	Glazed, sl. ptosis	4
Responds only to loud call	Slurred	Marked Relaxation	Glazed, marked ptosis	3
Responds only to moderate prodding	Few Recog. Words	-	-	2
No response	-	-	-	1

Patients were then randomized to receive flumazenil 0.1mg/ml (20 patients) or placebo vehicle (10 patients) in 2ml increments every minute for five minutes or until a sedation score of 4 or 5 was obtained. Patients were assessed for level of residual sedation, nausea and vomiting, dizziness, other side effects, ambulatory function (finger-to-nose, sitting and progressive walking) and overall 'discharge- readiness' for 3 hours in the PACU. Age, weight, doses of fentanyl and midazolam, duration of surgery, systolic blood pressure (BP) on arrival in the PACU, BP change at 5 min were compared between groups using unpaired t-test. The change of the sedation score between 0 and 5 min in the PACU was analyzed utilizing the Mann-Whitney U test. The incidences of vomiting and spontaneous patient complaint of dizziness during the 3 hours after arrival in the PACU, as well as the percentages of patients that were assessed as 'discharge-ready' at 120 min after arrival in the PACU were analyzed by contingency tables. Statistical significance was considered at $P < 0.05$ level.

Results:

	Placebo	Flumazenil	P
Age in years	62 (13)	61 (13)	0.93
Weight kgs	76 (17)	73 (15)	0.66
Duration Surg(min)	18 (11)	16 (10)	0.70
Fentanyl ugm/kg	1.4 (0.4)	1.3 (0.3)	0.67
Midazolam mg/kg	0.18 (.06)	0.19 (.05)	0.29
SysBP arrival mmHg	111 (18)	117 (14)	0.31
Change BP at 5min	-1 (8)	17 (17)	0.003*
Sed score Time 0	1.8 (0.9)	1.4 (0.7)	
Change Sed at 5min	0.3 (0.5)	2.4 (0.8)	0.0001*
Vomiting %	50%	20%	0.09
Complain dizzy	10%	45%	0.06
Discharge Ready @ 2 hours	30%	70%	0.03*

Values are mean (S.D.) * Significant difference.

Discussion: The faster wake-up, higher percentage of 'discharge-ready' patients at 2 hours in the flumazenil group (with minimal side-effects) suggests the use of midazolam-based general anesthesia and subsequent antagonism with flumazenil may be a viable alternative for outpatient surgery in the future. The greater change in systolic blood pressure in the treatment group during the 5 minutes of drug titration probably reflects greater awareness, stimulation and pain in these patients as compared to controls. The degree of hypertensive response does not appear to be dangerous considering the initial PACU BP's. The trend toward less vomiting in the flumazenil group is of note as is the trend toward more 'dizziness' complaints in the flumazenil group. Further trials are warranted to confirm these results.

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Title: Morphine Requirements for Post-Operative Pain Relief Using Patient Controlled Analgesia; Comparison of Morphine Alone and in Combination with Promethazine

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Introduction

To date there is very little information concerning sedative-analgesic combinations delivered by PCA systems. Would such combinations allow a satisfactory level of post-operative pain relief to be achieved with lower morphine dosages and with a lower incidence of side effects. This study has been designed to try to evaluate the combined use of promethazine and morphine post-operatively, and to compare this to morphine alone administered by a PCA system in a comparable group of patients.

Methods

The study has been carried out on 20 Orthopaedic patients undergoing hip or knee replacement. This study was approved by the Institutional Human Investigation Committee. The patients were evaluated on the evening prior to surgery and their written consent to the study was obtained. The patients were given written information and instructions with regards to the aim of the study, and the patient was shown the Bard PCA pump and instructed in its operational use. The patients were pre-medicated with midazolam and further sedation was given in the Holding Room as deemed necessary. Patients were anesthetized using a balanced anesthetic technique. 5 micrograms of fentanyl were given on induction which was completed with surital 4 mg per kg and the patients intubated using pavulon 0.1 mg per kg. The patients were maintained on nitrousoxide, oxygen, and isoflurane. The patients were ventilated to normocapnia. Routine monitoring of vital signs, and additional monitoring as deemed necessary by the anesthesiologist were carried out. At the conclusion of the operation the patients were reversed with neostigmine and atropine and extubated. The patients were then taken to the Recovery Room and monitored according to standard procedures.

The patients were randomly assigned to one of two groups. Group one patients received a solution containing morphine 1 mg per ml, and group two patients received a solution containing morphine 1 mg per ml plus promethazine 1 mg per ml. These solutions were administered by the PCA pump and standard giving set. On initiating the PCA, the patients received a bolus injection of 4 ml of one of the solutions. The PCA pump was then set to deliver 2 ml with a lock-out interval of 10 minutes. When the patients were stable, pain free, and able to follow instructions, they were returned to the floor. The following observations and recordings were made on a standard flow sheet to be followed by the nursing staff, who were blinded as to the solution that was being used.

1. Standard cardiovascular/respiratory parameters for post-operative patients.
2. Subjective recording of the patients pain complainant on a scale of 1-5.
3. The hourly volume of solution used.
4. The sedation level on a scale of 1-4.
5. Side effects. Nausea, emesis, pruritus, and urinary retnetion.

At the end of 48 hours the data was collected and analyzed by statistical analysis.

Results

Twenty patients have been evaluated, 10 patients in each group. There were no cases of hypertension, or other cardio-vascular complications and no problems with respiratory depression. There was no difference in the side-effects with regard to nausea, vomiting, pruritus, or urinary retention between the two groups. The hourly morphine usage, sedation scores, and pain scores are presented in the table.

Results Table

	Group I - Morphine	Group II Mo + Promethazine
Morphine mg/Hour (±SD)	2.6 ± 0.37	2.01 ± 1.59^{NS}
Sedation	1.17 ± 0.18	1.77 ± 0.9 *
Pain Score	$2.32 + 0.6$	$2.1 + 0.9^{NS}$

*P <0.05 Group II compared to Group I.

Discussion

The use of phenothiazines in conjunction with narcotics has a long history.[1] With regard to analgesia it has been reported that many of the phenothiazines have analgesics effects, particularly chlorpromazine, promazine and methotrimeprazine. The data on promethazine is conflicting, and this perhaps is due to a biphasic reaction with an initial decrease followed later by an increase in pain thresholds.[2,3] Promethazine would appear to be relatively free of side-effects explaining its long use; alone it has no significant effect on respiration, but may prolong narcotic induced respiratory depression. Promethazine also diminished reflex control of the circulation, but its effects are not as profound as those with promazine and many publications attest to the satisfactory sedation achieved by combinations of promethazine and narcotics.[4] The preliminary data from this pilot study would indicate that the use of promethazine may decrease the amount of morphine required, but at the cost of increased sedation and without any change in the patients pain perception. Circulatory instability or respiratory depression were not enhanced by this combination of drugs in the patients studies. A low incidence of other side-effects was recorded which was similar for the two groups.

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Title: Does Chronic Opioid Antagonism Alter Analgesic and Anesthetic Responses

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Introduction

It has been shown that the chronic blockade of opioid receptors by Naltrexone produces marked changes in endogenous brain opioids and opioid receptors.[1,2] It has also been demonstrated that these effects are associated with an enhanced sensitivity to subsequently administered opioids.[3] The evidence regarding the interaction of anesthetics with endogenous opioid systems is conflicting.[4] The aim of this study therefore was to measure analgesic responses following withdrawal of the opioid antagonist Naltrexone and to evaluate whether this altered anesthetic potency.

Methods

The experiment was approved by the Institutional animal investigation committee of the University. Four groups of female sprague-dawley rats (n=10 per group-weighing 200-250 grams were maintained on Purina Rat Chow and water ad-libitum. Two groups were treated with Naltrexone-60 mg for 7 days by the subscapular implantation method.1 The two other groups were treated identically except that placebo pellets were used. In all groups the pellets were removed on the eighth day and the animals allowed to recover. On the ninth day the animals were evaluated for analgesic responses using the tailflick test.[5] The halothane MAC was then determined for each animal by the method described by White, et al.[6] One group of the Naltrexone animals and one group of the placebo animals were also administered 2 mg/kg of morphine intraperitoneally after the first tailflick response had been measured. Their analgesic responses were then remeasured and the halothane MAC determined. The animals were then sacrificed.

Results

The chronic treatment of rats with the narcotic antagonist Naltrexone and its subsequent removal lead to a significant increase in the analgesic response as measured by the tailflick test when compared to placebo. The relative analgesia demonstrated had no significant bearing on the response to anesthesia as measured by the halothane MAC which was not significantly different in the two groups. (Table 1) The second part of this experiment demonstrates that animals treated in the same way were made sensitive to exogenous opioids in this case morphine, but this was not reflected in any further reduction in the halothane MAC value which remained the same between the Naltrexone and the placebo groups. (Table 2)

TABLE 1	Naltrexone	Placebo
Analgesia (secs:mean + S.D.)	3.4 ± 0.66	2.3 ± 0.26*
Halothane MAC	0.86 ± 0.07	0.91 ± 0.06^{NS}

*Placebo < 0.01 vs Naltrexone

TABLE 2	Naltrexone Morphine	Placebo Morphine
Analgesia 1 (secs:mean ± S.D.)	3.4 + 0.6	2.2 + 0.18*
Analgesia 2	21.7 + 11.5	7.8 + 4.6+
Halothane MAC	0.74 + 0.16	0.80 + 0.12NS

* Placebo < 0.01 vs Naltrexone
+ Placebo < 0.01 vs Naltrexone NS Not Significant

Discussion

The chronic interposition of either an opioid agonist or antagonist between the endogenous opioid and its receptor appear to have very different effects. Chronic blockade by morphine leads to an increase in the opioid receptor population. This parallel effect may account in part for tolerance and is of brief duration following withdrawal. Opioid antagonism however, leads to a more sustained increase in opioid receptor numbers following withdrawal. Opioid antagonism however, leads to a more sustained increase in opioid receptor numbers following withdrawal. Also, it is suggested that endogenous opioid release is decreased by morphine and that this may be mediated in part by the parallel increase in opioid receptors excerting tonic suppression. Further, this tonic inhibition may be reversed by opioid antagonism and may facilitate endorphin release. Chronic opioid antagonism causes a sustained increase in endorphins even following withdrawal. The effects of the agonist compared to those of the antagonist may therefore represent an uncoupling process. Increased endorphin levels may account in part for the analgesia by tailflick and an increase in opioid receptor population account for the super sensitivity to morphine as demonstrated in this experiment. Agonist/antagonist manipulation of this system maybe important in the clinical areas of pain management and addiction.

The relationship of analgesia to anesthesia has been less clearly defined: Certainly where chronic opioid blockade is concerned there is very little information. In this model, we were unable to demonstrate any parallel effect on anesthesia requirement where analgesia had been demonstrated. Moreover, despite a marked increased in analgesic response to morphine there was no reduction in the Halothane Mac values for Naltrexone treated rats. This seems to indicate a remarkable difference in mechanisms such that anesthesia is independent of endogenous opioid systems.

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Title: SAFETY AND EFFICACY CF ALFENTANIL IN CHILDREN LESS THAN ONE YEAR OF AGE*

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Introduction: The inclusion of narcotics as a part of neonatal anesthesia has been controversial. Past studies of narcotics for use in pediatric anesthesia have demonstrated an increased sensitivity to respiratory depression in neonates (1). As a result, narcotics have usually been avoided in children less than one year of age. Consequently, inhalational anesthesia has been the most commonly used method for anesthetizing this age group. The purpose of this study was to evaluate the safety and efficacy of alfentanil in infants less than 1 year of age undergoing outpatient inguinal surgery.

Methods: After our institution's Human Rights Committee approval and the written, informed consents of parents were obtained, 30 ASA I-II patients scheduled for bilateral inguinal herniorrhaphies were randomized into 2 groups. Both groups underwent inhalation induction via mask with halothane/N_2O 70%/O_2 30%. After the induction of anesthesia, atracurium 0.5 µg/kg and atropine 0.1 µg (total) were administered intravenously to prevent chest wall rigidity, facilitate endotracheal intubation, and prevent bradycardia, respectively. In group I halothane was discontinued and alfentanil, 50 µg/kg, was administered; supplemental alfentanil boluses (10 µg/kg) were given in response to hemodynamic changes greater than 20% above baseline. In group II halothane was maintained and adjusted to the anesthetic needs. All infants were intubated and controlled ventilation was maintained throughout the surgery.

Heart rate and blood pressure were recorded on admission to the outpatient surgical facility (T1), arrival in the OR (T2), 3-minute post-atropine (T3), 1 minute pre- and post-alfentanil injection (T4,5), 1 minute pre- and post-intubation (T6,7), 1 minute pre- and post-skin incision (T8,9), as well as throughout the recovery room stay. All data were analyzed with analysis of variance; statistical significance was considered for $p < 0.05$.

Postoperative pain was compared between the two groups utilizing a 4-point scale (0-4 = comfortable to severe pain). The postoperative incidence of vomiting was also compared on a 4-point basis (0-3 = none to productive vomiting).

Results: There was no difference between the groups with regards to age and weight. One patient in group II and no patients in group I experienced hypotension. There was no significant difference between the groups with respect to heart rate. However, systolic blood pressure was significantly higher in the alfentanil group following the incision (T8) (see Figure). To achieve hemodynamic stability, the range of alfentanil boluses required was 1.5-2.5 µg/kg/min. No postoperative respiratory depression occurred in either group in the recovery room.

During the post-anesthetic period, patients from both groups were admitted with pain scores of ≤ 1 (mild pain) which responded within the initial 5 minutes to cuddling. There was no statistical difference in the post-anesthesia pain scores between the 2 groups. Out of the 30 patient study, only one patient (from the alfentanil study group) demonstrated retching. One patient had apnea following removal of the endotracheal stimulus, but responded to 1 µg/kg of Narcan.

Discussion: Inhalational anesthetics, in particular halothane, have served as the primary agents for anesthetizing infants and neonates. The use of volatile agents is not without attendant risks, including myocardial depression and hypotension. We evaluated the hemodynamic effects of alfentanil during stress periods of surgery in infants and compared it to a group of infants anesthetized with halothane. Both groups had adequate residual analgesia postoperatively. The repeat boluses required an average of 1.5-2.5 µg/kg/min. We conclude that alfentanil is a safe anesthetic. Initial doses of 50 µg/kg may not be enough to prevent the stress responses of intubation and surgery. Higher initial doses, more frequent boluses, or a continuous infusion may be more beneficial.

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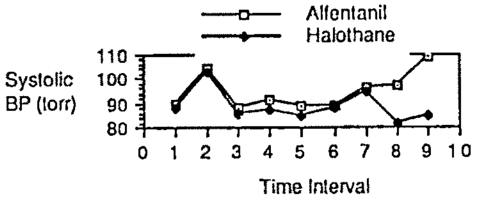

Title: CORRELATION OF ASPIRIN INDUCED CHANGES IN BLEEDING TIME, PLATELET AGGREGATION AND SONOCLOT COAGULATION ANALYSIS IN HUMANS

Authors: S. K. Samra, M.D., R. Harrison, M.D., D. E. Bee, Ph.D, V. Valero, M.D.
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Introduction:

With an increasing number of surgical patients taking aspirin (for prevention of myocardial infarction and stroke), there is a need for a simple and practical bedside test for evaluation of platelet function prior to administration of regional anesthesia. The "State of the Art" tests currently in use for this purpose are a template bleeding time (BT) and platelet aggregation studies (PA). Both are difficult to obtain for emergency surgery in most hospitals. We have evaluated the performance of a new device, Sonoclot® Coagulation Analyzer (Sienco, Inc.) against these two tests. This investigation was designed to study (a) variations in prolongation of bleeding time after aspirin intake and b) correlation between bleeding time, platelet aggregation and Sonoclot® graphs.

Methods:

After obtaining IRB approval and informed consent, 22 subjects (11 males and 11 females) were studied. All denied any history of abnormal bleeding and consumption of any other medications. In each subject, BT was done and venous blood sample drawn for PA and Sonoclot® graph. Aspirin 325 mg b.i.d. was administered for two days and all tests repeated. PA response to arachidonic acid (AA), ADP, epinephrine, collagen (COLL) and ristocetin was studied. Sonoclot® analysis uses 0.4 cc blood mixed with kaolin in a cuvette. A vibrating probe measures changes in viscosity and generates a curve shown in Fig. 1. Initial flat portion of this curve correlates with activated clotting time followed by a rapid rise in viscosity due to fibrin polymer formation. Incorporation of platelets is indicated by "inflection" followed by a "peak" indicating completion of clotting and clot retraction (R_3). Numerical values for these variables can be calculated from the known chart speed. Numerical data for BT, PA (AA and COLL) and Sonoclot® graphs (TI, TP and R3) were subjected to a repeated measures analysis of variance to study the effect of aspirin, sex differences and any interaction between the two. Data were also subjected to a correlation analysis to study any correlation between the effect of aspirin on BT, PA and Sonoclot® variables.

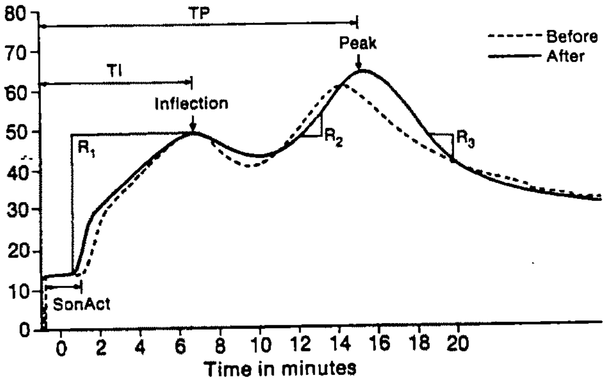
Results:

Mean values for BT, PA and Sonoclot® analysis are shown in Table 1. Mean value for BT increased significantly (P=0.0001) after aspirin, but great variability between subjects was noted. BT increased by only one minute or less in 3, and *decreased* in 3 others. Prolongation of bleeding time was more in males than females (50% vs. 25%) but this difference between the sexes was not statistically significant. PA showed significant decrease with AA (P=0.0001) and COLL (P=0.0002). Sonoclot® data did not show a significant difference either in morphology (Fig. 1) or numerical values of TI, TP and R_3. Significant variability between subjects was also noted for both PA and Sonoclot® data, as is evident by large S.D. No correlation between changes in BT, PA and Sonoclot® data was seen.

Discussion:

A significant decrease in PA with COLL and AA is in keeping with the well recognized effect of aspirin on cyclo-oxygenase and interference with PA.[1] It provides reliable evidence of aspirin ingestion by even those subjects who did not show a significant prolongation of BT in our study. Normal range of BT in our laboratory is from 2 to 9 minutes. Mean values of BT both before and after aspirin although showing statistically significant differences, remained within this range. Only 4/22 subjects had BT >9 minutes after aspirin and two of them had BT >9 minutes prior to aspirin. None of these subjects gave a history of abnormal bleeding. In a clinical setting, where one is not aware of BT prior to aspirin intake, BT after aspirin in our subjects would have been reported to be normal. These data support prior reports that although aspirin intake interferes with PA, it seldom presents the problem of excessive bleeding in patients with otherwise normal hemostatic mechanisms.[2] Our data show no correlation between PA and BT. Thus it further supports what has been previously contemplated that PA does not necessarily equate to *in vivo* events.[2] The fact that BT did not prolong to an abnormal value (>9 min.) in our study, makes it difficult to comment on the value of Sonoclot® in predicting which patients will develop aspirin related coagulopathy. We are currently evaluating this device in patients who are known to have markedly prolonged bleeding time. In one patient not included in this data set who was taking aspirin and alcohol simultaneously and had BT of 11 min., the Sonoclot® graph did not show an inflection thereby indicating poor platelet function.

Figure 1



Sonoclot graphs before and after aspirin in one subject whose bleeding time increased from 3.0 to 4.75 minutes.

TABLE I.

VALUES (MEAN ± S.D.) FOR BLEEDING TIME, SONOCLOT® GRAPHS AND PLATELET AGGREGATION BEFORE AND AFTER ASPIRIN

Parameter	Before Aspirin	After Aspirin	Value of P (Anova)
Bleeding Time (minutes)	5.32 ± 2.16	7.34 ± 2.15	0.0001
Platelet Aggregation:			
Arachidonic Acid	79.65 ± 33.40	12.1 ± 6.5	0.0001
Collagen	55.02 ± 37.05	17.14 ± 10.99	0.0002
Sonoclot Tracing			
TI (seconds)	320.91 ± 63.16	316.82 ± 62.44	0.68
TP (seconds)	565.45 ± 155.71	580.91 ± 157.57	0.51
R-3 (% min)	4.50 ± 1.77	4.14 ± 1.58	0.33

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Title: ENHANCEMENT OF SOMATOSENSORY EVOKED POTENTIALS BY ETOMIDATE - INVESTIGATION OF ITS SITE OF ACTION IN CATS

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Introduction:

In contrast with all clinically used anesthetics which are known to decrease the amplitude (ampl.) and increase the latency of cortical evoked potentials (CEP), etomidate (E) has been shown to increase the ampl. of CEP in humans.[1,2] Enhancement of CEP has been thought to be an undesirable property of E by some investigators[1] while others[2] consider it to be an advantage because it makes monitoring possible in patients with CEP of small ampl. This controversy can be rationally resolved if the locus of this action of E is identified. Since invasive electrophysiological monitoring is not feasible in humans, we have conducted this investigation in cats by recording evoked potentials simultaneously from sensory thalamus (VPL) and primary sensory cortex (S1), following stimulation of the tibial nerve. The aim of this study was to identify whether the locus of action of E is S1 or at subcortical levels. VPL was chosen because it represents the highest relay station for sensory input.

Methods:

Experiments were conducted in accordance with the standards approved by the animal use committee at our institution. Six adult cats were anesthetized with halothane (0.8-1%) in a mixture of 50% nitrous oxide in oxygen. Direct arterial blood pressure was continuously monitored. The mechanical ventilation was adjusted to maintain a steady end tidal CO_2 between 26-30 mm of Hg. Core temperature of 37°C (±1°) was maintained. The tibial nerve was exposed for stimulation. A small craniotomy was performed. A stainless steel recording electrode was stereotaxically introduced into the VPL nucleus of the thalamus and a ball electrode was placed on S1. The final position of electrodes was adjusted to achieve evoked potentials of maximum ampl. Once the optimal recording sites were identified, the exposed part of the brain was covered with a mineral oil-vaseline solution to prevent heat loss and dessication. Stimulating parameters were held constant throughout each experiment. After a steady state of anesthesia had been maintained for at least 2 hours, control CEP and thalamic potentials were recorded. Etomidate 1 mg/kg was given intravenously and evoked potentials recorded after 5, 10, 15, 20, 30, 40, 50 and 60 minutes. A second dose of E, 3 mg/kg was then given and records obtained at the above intervals. Two replications of evoked potentials in response to fifty stimuli were averaged at each time interval. The maximum ampl. of both CEP and thalamic potentials were measured and their latency noted. Values for ampl were normalized as a percentage change from control tracings which were considered as 100%. Numerical data thus obtained were statistically analyzed by using a two-way analysis of variance.

Results:

Effect of E on the ampl. of CEP and thalamic potentials is shown in Figure 1. Etomidate caused a dose related increase in CEP ampl. and the difference between the two doses was significant ($P<0.01$). An increase in ampl. after 1 mg was significant ($P<0.02$) for the first thirty minutes with gradual return towards control values. Increase in CEP ampl. after 3 mg/kg E persisted throughout the study period ($P<0.01$). Ampl. of thalamic potentials did not show a significant change ($P=0.107$) after administration of E. Etomidate also caused an increase in the latency of CEP. As shown in Table I, an increase in the latency of CEP was apparent from 5 to 30 minutes after 1 mg/kg of E ($P<0.01$) and for the entire duration of each experiment after 3 mg/kg dose. Latency of thalamic potentials remained unchanged (1 mg) or showed a minimal increase (3 mg).

Discussion:

Our findings of an increase in the ampl. and latency of CEP after etomidate injection are similar to those previously reported in humans.[1,2] Lack of significant change in amplitude and latency of thalamic potentials suggests that the stimulating effect of E is at the level of primary sensory cortex. It has been traditionally taught that myoclonus commonly seen in patients during induction with E is a result of disinhibition of subcortical structures. Our data show that at least in the sensory system, E has no effect at subcortical levels. Our data also suggest that neural generators for CEP are located in S1 rather than the thalamus, as previously suggested by some investigators.[3]

Figure 1. EFFECT OF ETOMIDATE ON AMPLITUDE (MEAN ± S.E.) OF CORTICAL AND THALAMIC EVOKED POTENTIALS

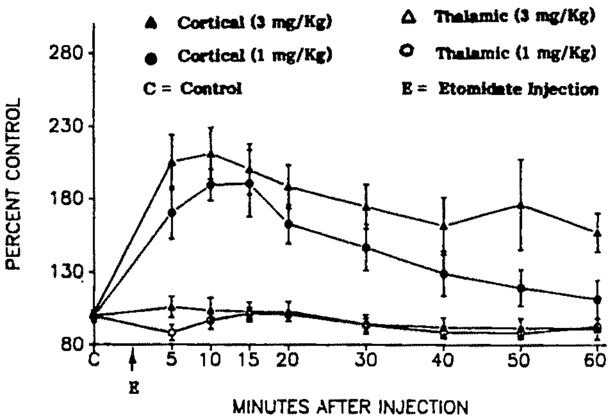

TABLE I.

Effect of Etomidate on Latency (mean ± S.D.) of Cortical and Thalamic Evoked Potentials

LATENCY IN MILLISECONDS				
TIME	CORTICAL POTENTIALS		THALAMIC POTENTIALS	
	Etomidate 1 mg	Etomidate 3 mg	Etomidate 1 mg	Etomidate 3 mg
Control	14.86 ± 1.05	14.66 ± 0.78	9.86 ± 0.27	9.72 ± 0.30
5 min.	16.49 ± 1.70	16.99 ± 1.43	9.92 ± 0.31	9.97 ± 0.56
10 min	16.58 ± 1.97	16.95 ± 1.37	9.91 ± 0.32	10.07 ± 0.38
15 min	16.37 ± 2.19	16.84 ± 1.41	9.90 ± 0.32	10.11 ± 0.34
20 min	16.30 ± 2.14	17.00 ± 1.73	9.90 ± 0.33	10.16 ± 0.56
30 min	16.59 ± 2.78	16.82 ± 1.59	9.88 ± 0.34	10.24 ± 0.48
40 min	14.98 ± 0.86	16.35 ± 1.58	9.86 ± 0.32	10.23 ± 0.49
50 min	14.70 ± 0.74	16.44 ± 1.41	10.04 ± 0.43	10.21 ± 0.51
60 min	14.70 ± 0.75	16.18 ± 1.72	9.83 ± 0.32	10.10 ± 0.34

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TITLE: **HYPERTENSIVE PATIENTS DO NOT HAVE INCREASED BLOOD LOSS DURING TOTAL HIP REPLACEMENT UNDER EPIDURAL ANESTHESIA AND CONTROLLED HYPOTENSION**

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Introduction

Epidural anesthesia has been used to minimize blood loss during total hip replacement(THR).[1] Hypertensive patients might be expected to have a greater intraoperative blood loss than patients without hypertension. However, it is not known whether a preoperative diagnosis of systemic hypertension results in greater intraoperative blood loss when patients are managed with epidural anesthesia and controlled hypotension.[2,3]

Methods

Approval of the Institutional Review Board was obtained to prospectively study 100 patients undergoing THR who required pulmonary artery monitoring for medical reasons. 50 patients (50%) had a preoperative diagnosis of systemic hypertension. Patient monitoring also included ECG, 20 ga. radial artery catheter, and pulse oximetry. Lumbar epidural anesthesia, using bupivacaine, 0.75%, produced a sensory level T1 to T4 and decreased mean arterial pressure (MAP) from baseline 102 ± 18.1 mm Hg to 58.5 ± 9.5 mm Hg (mean ±S.D.) ($p<.001$). Controlled hypotension was then maintained by infusion of a vasopressor ($n=68$), sodium nitroprusside($n=6$), or both ($n=24$). Measurements of MAP, cardiac index (CI), heart rate (HR), pulmonary artery diastolic pressure (PAD), right atrial pressure (CVP), and arterial blood gases were taken at the baseline and at 5 separate intervals during controlled hypotension. Stroke volume (SV) and systemic vascular resistance (SVR) were calculated. Estimated blood loss (EBL) was determined by the operating room nurse by weighing sponges and by keeping a strict accounting of irrigation and suctioned fluids. Statistical analysis was performed using ANOVA and two-group, two-tailed t-test.

Results

Baseline hemodynamics and blood gases are shown in Table 1. The effect of controlled hypotension on hemodynamic parameters and blood gases is shown in Table 2. Baseline MAP was significantly higher in hypertensive patients, but, during controlled hypotension, there was no significant difference in MAP between groups. There was no significant difference in EBL between hypertensive and non-hypertensive patients (Table 3).

Discussion

We did not study a control group of patients with epidural anesthesia without controlled hypotension. However, others have established that blood loss can be reduced by using controlled hypotension[2]. We conclude that, in the setting of epidural anesthesia and controlled hypotension, and inside the range of hemodynamics observed, a preoperative diagnosis of systemic hypertension does not predispose patients to higher blood loss during THR.

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Table 1. Baseline Hemodynamics and Arterial Blood Gases

	HTN Mean ±S.D.	No HTN Mean ±S.D.	P <
MAP (mm Hg)	106.6 ±19.3	98 ± 16.0	0.05
CI ($l/min/M^2$)	3.15 ± 0.66	3.38 ±0.88	n.s.
HR (B/min)	75.9 ±15.9	75.8 ±11.4	n.s.
CVP (mm Hg)	5.7 ±3.2	5.6 ±2.8	n.s.
PAD (mm Hg)	12.8 ±4.8	12.2 ±3.8	n.s.
SV (ml)	78.4 ±23.1	73.9 ±23.3	n.s.
SVR (dynes $cm^2 sec^{-5}$)	1459 ±486	1354 ±460	n.s.
P_aO_2 (mm Hg)	169.4 ±53.4	192.6 ±51.1	0.05
P_aCO_2 (mm Hg)	39.8 ±4.7	40.0 ±5.2	n.s.
BE	1.9 ±3.1	0.8 ±2.6	n.s.

Table 2. Measurements During Controlled Hypotension†

	HTN Mean ±S.D.	No HTN Mean ±S.D.	P <
MAP (mm Hg)	61.2 ±9.1	58.4 ± 7.2	n.s.
CI ($l/min/M^2$)	2.53 ± 0.54	2.79 ±0.78	n.s.
HR (B/min)	70.2 ±15.5	70.3 ±14.1	n.s.
CVP (mm Hg)	3.5 ±2.8	3.8 ±2.7	n.s.
PAD (mm Hg)	9.6 ±3.8	9.9 ±3.5	n.s.
SV (ml)	69.2 ±24.0	71.7 ±21.3	n.s.
SVR (dynes $cm^2 sec^{-5}$)	1083 ±381	987 ±299	n.s.
P_aO_2 (mm Hg)	150.7 ±48.6	165.8 ±44.0	n.s.
P_aCO_2 (mm Hg)	41.3 ±5.1	42.2 ±4.3	n.s.
BE	-0.6 ±2.1	-0.9 ±2.2	n.s.

† Average of 5 measurements during controlled hypotension.

Table 3 Estimated Blood Loss in Hypertensive vs. Non-Hypertensive Patients

	EBL (ml) Mean ±S.D.
HTN	344 ±238 §
No HTN	343 ±363 §

§ Difference between groups n.s.

Title: EFFECTS OF ORGAN PRESERVATIVE SOLUTION ON PLASMA GLUCOSE LEVELS: A COMPARISON BETWEEN COLLINS' SOLUTION AND UNIVERSITY OF WISCONSIN SOLUTION FOR ORTHOTOPIC LIVER TRANSPLANTATION

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Introduction: Intraoperative glucose regulation has been a concern during orthotopic liver transplantation (OLT). Theoretically the patient could be at risk for hypoglycemia during the anhepatic phase.[1] However, hypoglycemia has not been reported. In fact, reperfusion has been observed to result in a large increase in plasma glucose (PG). This was attributed to the 60% glucose present in the enriched Collins' preservative which was flushed out of the donor liver.[2] University of Wisconsin solution (UWS) has been introduced as an organ preservative.[3] This differs radically from Collins' solution and contains no glucose (Table). The purpose of this study was to determine if the use of a glucose-free organ preservative solution containing insulin would predispose the OLT patient to hypoglycemia in the postreperfusion period.

Methods: We compared glucose levels in a series of 100 consecutive patients receiving Collins' solution preserved livers with levels from 52 consecutive patients who received livers preserved with UWS. Anesthesia consisted of isoflurane, fentanyl, lorazepam, and pancuronium. High-dose methylprednisolone was administered intravenously according to the immunosuppression protocol. Other than blood products, glucose-free plasmalyte-A (Travenol Inc., Deerfield, IL) was the only IV fluid administered during the transplant. PG concentrations were measured by the oxygen rate method utilizing a Beckman Glucose Analyzer 2 (Beckman Instruments, Inc., Brea, CA) at the following times: 1) baseline, 2) 5 minutes before the anhepatic phase, 3) 10 minutes after the anhepatic phase, 4) 5 minutes before reperfusion of the donor liver, 5) 10 minutes after reperfusion, 6) 70 minutes after reperfusion. Within groups, PG levels were compared using analysis of variance with Neuman-Keuls modification for multiple comparisons. PG levels in Collins' solution group were compared with the UWS group using a two-tail T-test. T statistics yielding P values less than 0.05 were considered significant.

Results: During phase I, PG increased significantly from 110 ± 46 mg/dl to 204 ± 60 mg/dl in the Collins' group ($P < 0.05$) and from 105 ± 47 mg/dl to 197 ± 55 mg/dl in the UWS group ($P < 0.05$). There was no difference between groups during this phase. No significant change in PG occurred during phase II nor were there any between-group differences noted. Reperfusion of the donor liver resulted in another significant ($P < 0.05$) increase in PG in both groups: from 201 ± 56 mg/dl to 384 ± 44 mg/dl in the Collins' group, and from 182 ± 44 mg/dl to 314 ± 54 mg/dl in the UWS group. Postreperfusion PG values were significantly ($P < 0.05$) higher in the Collins' group than in the UWS group. No significant change in PG occurred within the groups during the first 70 minutes following reperfusion. However, PG levels remained significantly higher in the Collins' group than in the UWS group ($P < 0.05$).

Discussion: Because UWS contains raffinose and insulin, instead of dextrose, we suspected that minimal increases in PG would occur upon reperfusion of the donor liver. During phase I, PG concentrations increased as described earlier.[2] Surgical stress, corticosteroids and anesthesia likely account for these observations. The reperfusion increase of PG in the UWS group is difficult to explain. Raffinose does not cross cell membranes and does not affect oxygen rate measurements of serum glucose. We also would expect the insulin present in the UWS to retard release of glucose from hepatocytes. It could be that the increase in PG at the time of reperfusion has little to do with the contents of the preservative. Perhaps the increase in PG is due to changes in cell permeability during harvest and storage which results in large amounts of glucose entering the recipient circulation.

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TABLE. Comparison of UW Solution with Modified Collins' Solution

UW solution	mmol/ml	Collins' solution	mmol/ml
K lactobionate	100	$K_2HPO_43H_2O$	57.5
$N_aKH_2PO_4$	25	HCl	15
Adenosine	5	$MgSO_4$	8
$MgSO_4$	5	$NaHCO_3$	10
Glutathione	3	Glucose	139
Raffinose	30	Mannitol	100
Allopurinol	1		
Insulin	100 μ		
Bactrim	0.5 ml		
Dialyzed HES	5 g/dl		

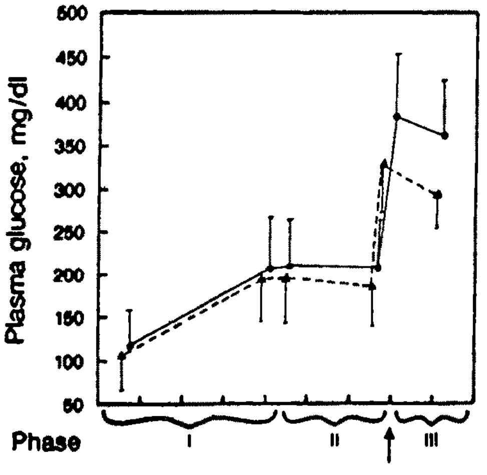

FIGURE. Mean plasma glucose concentrations during three phases of orthotopic liver transplantation comparing Collins' solution (solid line) with University of Wisconsin solution (broken line) as preservative medium. Phase I = from induction of anesthesia to removal of diseased liver; Phase II = anhepatic phase; Phase III = from reperfusion of transplanted liver (arrow) until end of procedure. Vertical lines = standard deviations.

THE EFFECTS OF PEEP AND INTRAOPERATIVE MODE OF MECHANICAL VENTILATION ON POSTOPERATIVE SPIROMETRY

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Introduction. Lung volume decreases shortly after induction of general anesthesia. Functional residual capacity (FRC) is reduced in 50% of patients 24 hours after anesthesia.[1] These changes lead to abnormal pulmonary gas exchange[2] and may contribute to morbidity. The effects of different modes of intraoperative mechanical ventilation on postoperative pulmonary function have not been studied.

This study was designed to determine 1) whether pulmonary changes associated with general anesthesia can be identified using bedside spirometry, and 2) if the intraoperative mode of mechanical ventilation or the use of PEEP affect postoperative pulmonary function tests.

Methods. 36 ASA I and II patients, without known lung disese, scheduled for non-emergent extremity surgery under general anesthesia were studied after giving informed consent and with the approval of the human subjects review committee. Bedside spirometry was performed preoperatively either the night before or the morning of surgery. Postoperative spirometry was performed the day after surgery. Measured parameters included forced vital capacity (FVC), forced expired volume in one second (FEV1), peak expiratory flow rate (PEFR), and the flow rate measured between 25% and 75% of the forced expiratory volume (FEV25-75). Patients were randomized to receive one of three modes of intraoperative mechanical ventilation. One group (IMV) received synchronized intermittent mandatory ventilation with a tidal volume of 12 cc/kg. Respiratory rate was adjusted to maintain an end-tidal CO_2 ($ETCO_2$) of 30-35 mmHg. A second group (PSV) was allowed to breathe spontaneously with inspiratory pressure support sufficient to maintain tidal volume at 12-15 cc/kg. The third group (IMV+PEEP) was ventilated as in the IMV group but with the addition of PEEP 10cm H_2O.

Patients received thiopental and succinylcholine prior to orotracheal intubation. Maintenance anesthesia consisted of isoflurane and nitrous oxide (50-70%) in oxygen. Intraoperative mechanical ventilation was performed with a Siemens 900C anesthesia machine. Perioperative narcotic analgesia was recorded but not specified by the protocol. One-way analysis of variance (ANOVA) was used to test differences among groups. Student's paired t-test was used to test preoperative versus postoperative spirometry data within groups, and the Chi-square test was used to test for differences in smoking among groups.

Results. Groups were similar in terms of age, height, weight, tobacco use, and duration of anesthesia. The mean elapsed time to postoperative spirometry testing was 20.9 ± 7.6 hours for all patients. (Table 1).

Table 2 displays spirometry data. Insignificant decreases in FVC and FEV1 occcured in all groups. Patients who received intraoperative PEEP had significantly improved PEFR (+12.7%) and FEV25-75 (+12.8%) compared to the other groups. Ten of 13 patients in the IMV+PEEP group had increased postoperative PEFR and FEV25-75. In contrast, of the patients ventilated without PEEP, only 10 of 23 had increased postoperative PEFR and only 6 of 23 had increased FEV25-75.

Discussion. Closure of small airways with a reduction of functional residual capacity (atelectasis) during general anesthesia may be a cause of diminished postoperative pulmonary function. Compared to other groups, patients who received 10 cm H_2O PEEP had better postoperative PEFR and FEV25-75. Intraoperative ventilation with 10cm H_2O PEEP more effectively preserves pulmonary function than intermittent mandatory ventilation or pressure support ventilation without PEEP. The majority of the study patients were hospitalized and bedridden during the days prior to surgery which could have contributed to development of atelectasis. This may help to explain improvements in FEV25-75 and PEFR after the intraoperative use of PEEP.

Table 1. Study Patients Mean (S.D.)

	IMV n=11	PSV n=12	IMV + PEEP n=13
Sex (m\f)	8\3	12\0	8\5
Age (yrs)	36.1 (9.5)	32.7 (9.9)	44.3 (11.5)
Height (cm)	176.9 (10.3)	177.0 (5.3)	168.4 (12.6)
Weight (Kg)	84.5 (23.2)	75.5 (9.5)	74.2 (18.3)
Cigarette use:			
smokers	6	4	9
(pack-yrs)	26.8 (22.4)	8.8 (1.5)	18.6 (12.7)
Duration of anesthesia (hrs)	3.2 (2.1)	2.5 (1.2)	2.7 (1.1)
Time to postop testing (hrs)	19.6 (7.2)	21.1 (8.6)	21.8 (7.0)

Table 2 Pulmonary Function Data Mean (S.D.)

	IMV	PSV	IMV + PEEP
FVC (L)			
preop	4.2 (0.9)	4.3 (0.7)	3.8 (1.0)
postop	3.8 (0.9)	4.1 (0.8)	3.7 (1.3)
Percent change	-7.8	-4.1	-6.7
FEV1 (L)			
preop	3.7 (0.9)	3.7 (0.7)	3.5 (0.9)
postop	3.4 (0.9)	3.6 (0.7)	3.3 (1.2)
Percent change	-8.3	-3.8	-5.1
PEFR (L/sec)			
preop	8.8 (2.8)	8.8 (3.8)	6.8 (2.6)
postop	8.0 (3.3)	8.1 (3.4)	7.6 (3.2)
Percent change	-8.7	-8.5	+12.7 *
FEV25-75 (L/sec)			
preop	7.1 (3.2)	7.3 (2.9)	5.3 (2.1)
postop	6.6 (3.4)	6.7 (3.0)	6.1 (2.9)
Percent change	-6.5	-9.9	+12.8 *

ANOVA Comparing differences among groups.
* $p < .05$

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TITLE: CEREBRAL BLOOD FLOW, $CMRO_2$, AND HEMODYNAMIC RESPONSES TO SEVOFLURANE: A COMPARISON WITH ISOFLURANE IN THE DOG

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INTRODUCTION: Sevoflurane (S) is a pleasant smelling ether volatile anesthetic with a lower blood gas solubility ratio than isoflurane (I) (0.60 vs. 1.41).[1] This suggests that S may be more advantageous than I for use in neurosurgical patients where rapid emergence is deemed desirable. We have previously demonstrated that the metabolic depression and cerebral blood flow (CBF) responses to 1 MAC S and I were similar in rabbits already anesthetized with morphine and nitrous oxide.[2] We have now compared the CBF and cerebral metabolic rate for oxygen ($CMRO_2$) effects of S and I in dogs anesthetized with only graded doses of either volatile agent.

METHODS: Following approval by the institutional animal care committee, 12 mongrel dogs of either sex were anesthetized by mask with either S (n=6) or I (n=6) and their tracheas intubated. Animals were paralyzed with pancuronium and their lungs ventilated mechanically. Ventilation was controlled and normocapnia (End-Tidal (ET) carbon dioxide (CO_2)= 35-40 mm Hg) was maintained throughout the remainder of the study. Surgical preparation was carried out during 1.5 MAC anesthesia. CBF was measured directly using the venous outflow method which necessitated placing a cannula in the sagittal sinus and measuring the effluent blood flow with timed aliquots. The cerebral metabolic rate for oxygen ($CMRO_2$) was determined as the product of CBF and the arterial-sagittal sinus oxygen content difference. Monitored variables consisted of a bipolar fronto-occipital EEG, mean arterial pressure (MAP), heart rate (HR), pulmonary artery pressure (PA), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), temperature (servocontrolled to 37°), ET volatile anesthetic, ET CO_2, CBF and $CMRO_2$.

Following the surgical preparation, animals were left undisturbed for 30 min at 0.5 MAC ET volatile anesthetic (0.64% I or 1.55% S). All monitored variables were then recorded and the ET level increased to 1.5 MAC and all variables similarly recorded. This sequence was repeated during EEG burst suppression (BS) and finally after returning to 0.5 MAC. Phenylephrine was infused as necessary to keep MAP > 60 mm Hg during the administration of the highest concentrations of volatile anesthetic. At the conclusion of the study, the animals were killed and the brains removed for weighing. Hemodynamic parameters, CBF and $CMRO_2$ data within groups were compared using an ANOVA and Dunett's t-tests when indicated. $p < 0.05$ was considered statistically significant.

RESULTS: Burst Suppression was achieved with similar MAC multiples of S and I, 2.14 MAC and 2.18 MAC respectively. Both S and I caused dose dependent significant decreases in MAP, but C.O. was not significantly affected (Table 1). Increasing concentrations of S or I did not significantly alter CBF compared to CBF during 0.5 MAC (Table 1). However, $CMRO_2$ was significantly decreased during BS compared to 0.5 MAC in both groups (Figure 1). All hemodynamic parameters as well as $CMRO_2$ during the second exposure to 0.5 MAC were not different compared to those during the first exposure to 0.5 MAC. Two animals in the I group and 1 animal in the S group required phenylephrine to maintain MAP above 60 mm Hg during the administration of the highest concentration of volatile anesthetic (i.e. BS).

DISCUSSION: These data demonstrate that both S and I decrease $CMRO_2$ in a dose dependent fashion while leaving global CBF relatively unaffected. The decreases in $CMRO_2$ during BS compared to 0.5 MAC were significant for both I and S. These observations agree with an earlier study in anesthetized rabbits in which S and I appeared indistinguishable in terms of their effects on CBF and $CMRO_2$.[2] However, the present study excluded the use of nitrous oxide or other background anesthetic agents which might alter the cerebrovascular response to volatile anesthetic administration.[3] The hemodynamic responses were similar in response to the administration of the two drugs. Thus, properties of I that make it desirable for use in neurosurgery such as a negligible effect on CBF and a potent cerebral metabolic depressent effect appear to be shared by S.

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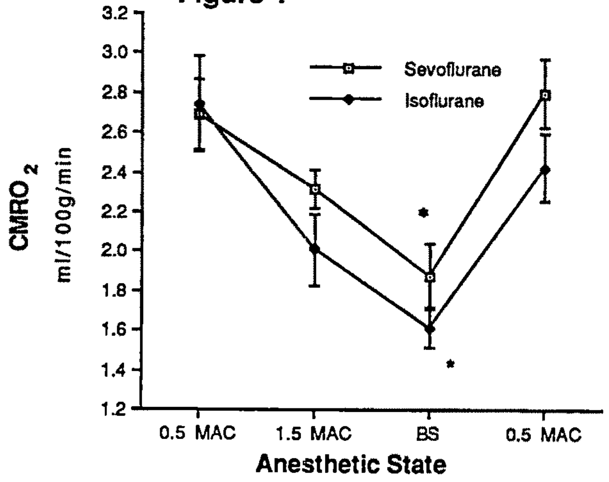
Figure 1



Cerebral metabolic rate for oxygen ($CMRO_2$) response to the administration of Sevoflurane or Isoflurane. All data Mean ± S.E.M. * = Significant ($p<0.05$) decrease compared to value obtained during 0.5 MAC.

Table 1- Cerebral Blood Flow and Cardiovascular Data

Anesthetic State\	0.5 MAC		1.5 MAC		BS	
Volatile Anesthetic	Sevo	Iso	Sevo	Iso	Sevo	Iso
Measured Variable						
CBF (ml•100g•min)	57±14	66±13	53±10	70±25	50±14	56±21
MAP (mm Hg)	117±13	140±38	93±16*	92±20*	76±17*	71±15*
C.O. (Liters/min)	1.9±.7	1.5±.7	1.4±.5	1.7±.7	1.5±.9	1.3±.5

CBF=Cerebral Blood Flow, MAP= Mean Arterial Pressure, C.O.= Cardiac Output. All data expressed as Mean±S.D. * = Statistically different from value during 0.05 MAC. $p<0.05$. Sevo=Sevoflurane, Iso= Isoflurane, BS=Burst Suppression.

TITLE:

THE EPILEPTIC PROPENSITY AND MAC OF SEVOFLURANE IN DOGS: A COMPARISON WITH ENFLURANE

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INTRODUCTION: Sevoflurane (S) is a pleasant smelling ether volatile anesthetic with a low blood gas solubility ratio which will soon undergo clinical testing in the United States. Because some ether volatile anesthetics, notably enflurane (E), have been shown to cause sustained seizure activity particularly in the presence of hypocapnia and/or auditory stimuli,[1] it is important to know if S might have a similar propensity. Therefore, we have determined MAC of S and the ability of S to cause EEG or gross motor evidence of seizure activity in dogs and have compared these effects to those of E.

METHODS: Following institutional animal care committee review and approval, 8 mongrel dogs of either sex were anesthetized by mask with either S (n=5) or E (n=3) and intubated without the aid of muscle relaxants. MAC was determined by the "up and down" method using a tail clamp as the stimulus.[2] End-Tidal (ET) volatile anesthetic was measured with an infrared analyzer using gas drawn from the proximal end of the endotracheal tube. Animals were ventilated for a minimum of 15 min at each ET volatile anesthetic level. Ventilation was controlled and normocapnia (ET carbon dioxide ($PaCO_2$)= 35-40 mm Hg) was maintained throughout the MAC study. Monitored variables consisted of a bipolar fronto-occipital EEG which was recorded continuously, mean arterial pressure, heart rate, ET volatile anesthetic and ET CO_2.

Following MAC determination, animals anesthetized with S were maintained for 15 min at 1. 5 MAC, 2.0 MAC, and 2.5 MAC S in escalating doses during normocapnia (ET CO_2=35-40 mm Hg) and hypocapnia (ET CO_2=15-20 mm Hg) and in the presence of intense auditory stimuli. Animals anesthetized initially with E were equilibrated only at 1.5 and 2.0 MAC. Following this initial exposure, E or S was discontinued and the other agent introduced and maintained at ET concentrations of 1.5 and 2.0 MAC during both normocapnia and hypocapnia and in the presence of auditory stimuli. In this way each animal was exposed to both S and E. The sequence of exposure to E or S was varied on an alternating basis. Seizure activity was defined by the presence of high amplitude, high frequency EEG activity associated with gross muscular moving of the animal.

RESULTS: Anesthetic induction with S was rapid and smooth in all animals. MAC of S was 2.10±0.23 % and MAC of E was 2.66±0.36%. Exposure to E at both ET levels was associated with seizure activity during hypocapnia. This seizure activity could always be elicited by auditory stimuli and was frequently sustained particularly during 1.5 MAC. In contrast, only one animal receiving S demonstrated any evidence of seizure activity. That animal had received E first and demonstrated only a brief EEG discharge associated with upper limb twitching lasting a few seconds during 2.0 MAC S administration during normocapnia which was not elicited by auditory stimuli. Further attempts to elicit seizure activity in that animal, including the institution of hypocapnia and application of auditory stimuli were unsuccessful.

DISCUSSION: Our determination of E MAC agrees well with previous determinations in dogs.[3] Recently, S MAC has also been determined in dogs and our determination also agrees well with that report.[4] The present study clearly demonstrates that in contrast to E, S in concentrations up to 2.5 MAC causes neither EEG nor gross motor evidence of seizure activity in dogs that have been rendered hypocapnic and/or exposed to intense auditory stimuli. This property is important to document for any anesthetic which might be used for neurosurgical patients in whom sustained seizure activity could lead either to an imbalance in the oxygen supply/demand ratio or an increase in intracranial pressure. However, it must be emphasized that these data were obtained from dogs with normal brains and extrapolation of these data to animals or patients with intracranial pathology is unwarranted at the present time.

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TITLE: HEMODYNAMIC ACTIONS OF THE STEREOISOMERS OF THE α_2-ADRENERGIC AGONIST, MEDETOMIDINE IN CONSCIOUS DOGS.

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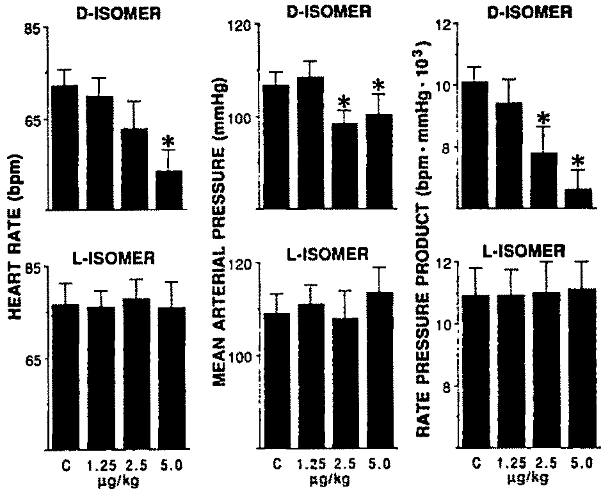
Introduction: Previous studies have demonstrated that the highly selective α_2-adrenergic agonist, medetomidine, produces a hypnotic anesthetic-like action on the central nervous system and diminishes the MAC of volatile anesthetics. Medetomidine has also been shown to alter systemic cardiovascular function *via* peripheral and central nervous system actions.[2,3] However, the majority of previous investigations have been conducted in anesthetized animals. The present investigation was designed to characterize the coronary and systemic hemodynamic actions of the D- and L-stereoisomers of medetomidine in chronically instrumented dogs with and without autonomic nervous system blockade.

Methods: After approval by the Institutional Animal Care Committee, dogs were instrumented with catheters for drug administration and measurement of aortic pressure, Doppler flow transducers for measurement of coronary blood flow velocity, a Transonic aortic flow transducer for measurement of cardiac output, and a left ventricular micromanometer for measurement of left ventricular pressure and +dP/dt, an index of left ventricular global contractility. Segment length gauges were implanted within the left ventricular subendocardium for determination of regional contractile function. Dogs were allowed to recover for 10 days following surgery. Three separate experimental groups were completed. On separate days, hemodynamics were continuously recorded in the conscious, unsedated state and after intravenous administration of D- or L- medetomidine (1.25, 2.5 and 5.0 µg/kg) in separate groups. Each drug was infused slowly over a period of 10 min with 60 min between increasing doses. Arterial samples were obtained during the control period and following drug administration for blood gas tensions. In the third group, after obtaining baseline hemodynamic measurements, autonomic nervous system blockade was accomplished by intravenous administration of hexamethonium (20 mg/kg), propranolol (2 mg/kg) and atropine methylnitrate (3 mg/kg). During a stable hemodynamic state, D-medetomidine (1.25 and 2.5 µg/kg) was administered as above. All data were compared to control using SAS software GLM followed by Duncans t-test and considered significant (*) when $p<0.05$.

Results: Administration of the D-isomer resulted in pronounced sedation at all doses. No change in respiratory rate or arterial blood gases occurred. An initial pressor response was followed by significant dose-related decreases in heart rate, mean arterial pressure and the rate-pressure product (Figure). No changes in left ventricular end diastolic pressure, +dP/dt, or coronary blood flow velocity occurred. In contrast to the D-isomer, the L-isomer produced inconsistent sedation. Additionally, no hemodynamic changes were observed (Figure). In the autonomically blocked group a significant decrease in arterial pressure and +dP/dt with a compensatory tachycardia occurred after blockade. While a pronounced sedative action of D-medetomidine was still observed after autonomic nervous system blockade, there was no change in heart rate, arterial pressure or the rate pressure product.

Discussion: The results of this investigation indicate that the isomers of medetomidine display stereospecificity for both production of sedation and alterations in hemodynamics. The D-isomer is the active isomer. The progressive decrease in heart rate, arterial pressure and rate pressure product produced by D-medetomidine are consistent with previous studies demonstrating a diminished sympathetic outflow mediated by activation of α_2-adrenergic receptors in the central nervous system. The lack of hemodynamic response to D-medetomidine after autonomic nervous system blockade supports such a concept. The ability of D-medetomidine to produce profound sedation, in combination with the favorable affect of this agent on systemic hemodynamics and lack of respiratory depression suggest a potential therapeutic role as a specific adjunct for anesthetic management.



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(This work was supported in part by NIH grant HL 36144 and VA Medical Research Funds)

Title: PROLONGED PROPOFOL/N_2O ANESTHESIA - HEMODYNAMIC, NEUROENDOCRINE AND RECOVERY FEATURES

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Introduction: Propofol (di-isopropyl phenol) has a rapid distribution half-life and high clearance rate, and has been shown to produce superior recovery following use for short procedures.[1] The objectives of this study were to compare the hemodynamic and neuroendocrine changes during, and the recovery quality and morbidity following prolonged propofol/N_2O/O_2 anesthesia, with conventional enflurane/N_2O/O_2 anesthesia in elderly patients undergoing peripheral vascular bypass surgery.

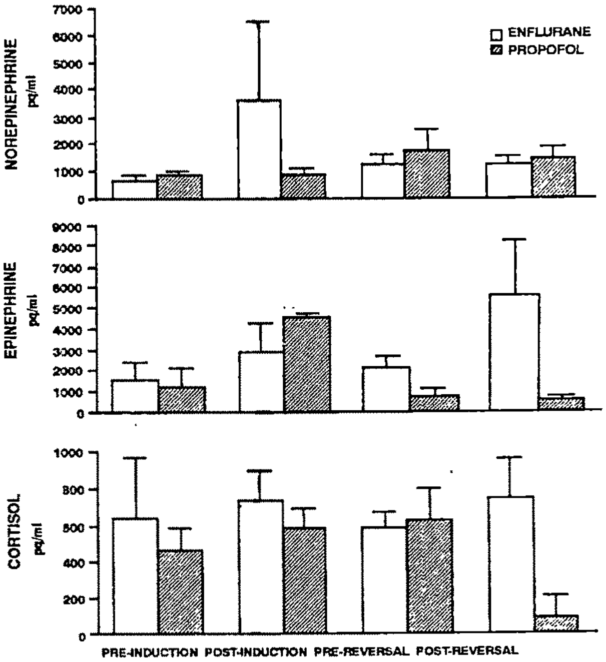
Methods: Following institutional ethics committee approval; and written informed consent 20 patients (mean age = 73.4 ± 6.7) presenting for peripheral vascular bypass surgery were randomly allocated to two groups. Group 1 patients were maintained on a continuous infusion of propofol, at 1-3 mg/kg/hr. Group 2 patients were maintained with enflurane 0.5-2%. Induction was identical in both groups, with propofol 2 mg/kg and vecuronium 0.1 mg/kg, followed by intubation and ventilation to normocapnia with 30% oxygen in nitrous oxide, which was maintained throughout.

Heart rate, blood pressure, oxygen saturation, end tidal capnography and temperature were recorded every 15 minutes. Blood samples were taken five minutes pre-induction, five minutes post-induction, ten minutes pre-reversal, and one hour post-reversal. These were immediately centrifuged and frozen, and later assayed for serum cathecholamines and cortisol.

Recovery was assessed by noting the time to wake up (TTWU), defined as the interval between reversal of anesthesia and spontaneous eye opening to verbal command; and by the Steward recovery scale at 5 and 15 minutes post-reversal. Morbidity was assessed by the presence of major cardiac or respiratory complications on the third post-op day.

Results: The two groups were comparable in terms of age, sex, weight and duration of surgery, for which the mean value was 4 hours and 5 mins ± 47 mins. Blood pressure and heart rate fell in both groups post-induction and remained at a lower level throughout surgery, with no significant difference demonstrable between the two groups.

Similarly there was no statistical difference in any of the cathecholamine or cortisol levels, between the two anesthetics, at any time point. The values for mean plasma norepinephrine, mean plasma epinephrine, and mean plasma cortisol at the four selected time points are depicted graphically:



The mean TTWU in the propofol group was 6 mins. 30 secs. ± 40 secs., and in the enflurane group 6 mins. ± 70 secs. This difference was not significant ($p>0.05$). The median Steward scores (max=6) at 5 and 15 mins in the propofol group were 6 and 6, in the enflurane group 5 and 6. Major complications had occurred by the third post-op day in two patients in the propofol group (pneumonia, acute LVF), and in one patient in the enflurane group (M.I.).

Discussion: Propofol has hitherto been used mainly for induction of anaesthesia, or by incremental bolus for short procedures. This study shows that propofol/N_2O/O_2 may be safely used for prolonged vascular procedures in elderly patients. It provides stable haemodynamic conditions, minimal change in the neuroendocrine response, and recovery and post-operative morbidity similar to that seen after a more conventional inhalational technique. The fall in cortisol noted post-reversal was not significant ($p>0.05$,t test), however a fall in cortisol after propofol anesthesia has been previously noted[2], and may warrent further investigation.

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Title: TRANSCONJUNCTIVAL OXYGEN MONITORING DURING EXPERIMENTAL CHANGES IN OXYGEN DELIVERY IN DOGS

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Introduction: The palpebral conjunctiva is a unique accessible tissue in which a capillary bed is separated from the epithelial surface by 2-3 cell layers. The surface oxygen tension of the palpebral conjunctiva($P_{cj}O_2$) may reflect the oxygen tension(PaO_2), oxygen content(CaO_2) and blood flow(CO) in the underlying capillary bed, because of the low tissue oxygen consumption rate and the lack of a barrier to oxygen diffusion.[1]

This study examined the ability of a transconjunctival oxygen monitor, consisting of a minature Clarke electrode mounted on an opthalmic conformer, to respond to experimental changes in oxygen delivery ($DO_2 = CaO_2 \times CO$).

Methods: Following institutional animal investigation committee approval, 20 adult greyhound dogs (weight 25.6 ± 4.1 kgs.) were anesthetised with sodium pentothal 20mg/kg, and maintained on a 20mg/kg/hr infusion. The trachea was intubated, and normocapnic controlled ventilation with O_2/N_2 instituted. The femoral artery was cannulated for pressure monitoring and arterial blood sampling. A pulmonary artery catheter was inserted for thermodilution cardiac output and mixed venous oxygen tension measurements. The transconjunctival oxygen sensor was calibrated and applied to the eye.

The 20 dogs were divided into two groups. In group 1 (n=10) the inspired O_2/N_2 mix was altered in increments to give an FiO_2 of 0.21,0.40,0.60,0.80, and 1.00. Following restabilisation at 0.21, the FiO_2 was reduced to 0.15,0.10 and 0.05. Cardiac output, oxygen content and delivery were calculated at each FiO_2, and the transconjunctival oxygen tension($P_{cj}O_2$) was measured.

In group 2 (n=10) the FiO_2 was kept constant at 0.30, and a normovolemic reduction in cardiac output was induced by progressivly increasing the pentothal infusion rate. CO, CaO_2, DO_2 and $P_{cj}O_2$ were measured after each reduction in CO.

The statistical significance of changes in PaO_2, CO and DO_2 with $P_{cj}O_2$ over a range of FiO_2 and CO values was evaluated by Pearson product moment correlation. Agreement between PaO_2 and $P_{cj}O_2$ was assessed by Bland and Altman's statistical method.

Results: PaO_2 and $P_{cj}O_2$ were positively correlated over a range of FiO_2 (r=0.99) and CO (r=0.57). There was no correlation between $P_{cj}O_2$ and CO or DO_2.

With CO constant (Group 1 dogs, Fig.1) $P_{cj}O_2$ approximated PaO_2 values in normoxic and hypoxic ranges. In the hyperoxic range the PaO_2 - $P_{cj}O_2$ difference progressively increased and the spread of $P_{cj}O_2$ values increased. During normoxia and hypoxia the mean PaO_2 - $P_{cj}O_2$ difference was -1.35mmHg, with limits of agreement (±2SD) of +33.7 and -36.7mmHg.

With constant FiO_2 and varying reductions in CO (Group 2 dogs, Fig.2) the mean PaO_2 - $P_{cj}O_2$ difference was 38.3mmHg, with limits of agreement of +97.5 and -27.3mmHg.

Fig.1

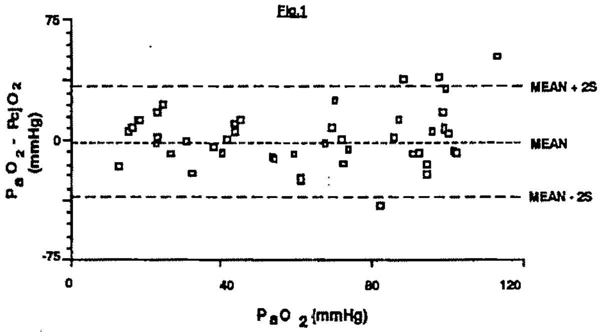
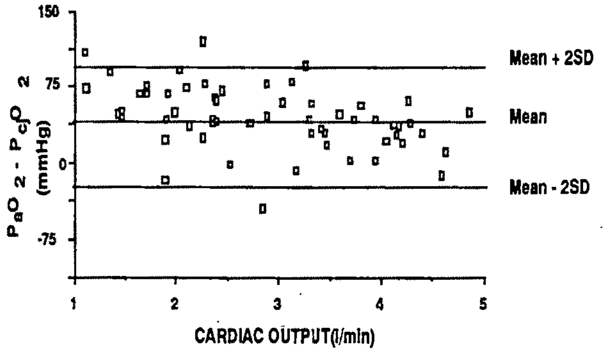


Fig.2



Discussion: Despite good correlation the wide limits of agreement for individual values make $P_{cj}O_2$ an unacceptable indicator of PaO_2 for clinical purposes. Variable reductions in conjunctival perfusion may have caused the increased PaO_2 - $P_{cj}O_2$ difference and wider spread of $P_{cj}O_2$ values seen during hyperoxia and normovolemic hypotension.[2]

$P_{cj}O_2$ may provide a simple noninvasive indication of PaO_2 in hypoxic or normoxic states in normovolemic hemodynamically stable patients, but modification of the method of measurement is required.

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DO "MOCK" ORAL PRACTICE EXAMINATION RESULTS CORRELATE WITH OTHER INDICES OF RESIDENT PERFORMANCE IN ANESTHESIA?

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Introduction: Evaluation of clinical competence in anesthesiology training programs is difficult. At our institution, clinical competence is assessed utilizing input from written examinations, clinical observation and daily resident performance evaluation cards (DRPEC). Previous work indicates poor correlation between indices of clinical performance and written test results (1,2). Recently we introduced regularly scheduled semiannual "mock" oral practice examinations (OPE) in our anesthesiology training program. The relationship of oral practice examination results with other indicators of resident performance is presently undescribed. This preliminary report examines how well overall and component scores from our first OPE correlated with results of in-training (ITE) and departmental examinations (DE) as well as with clinical competence scores derived from DRPEC at our institution.

Methods: The procedure for administering the OPE adhered closely to the ABA format for oral examinations. On two consecutive days, three pairs of faculty examined a total of 24 CA2 (n=10), CA3 (n=11) and CA4 (n=3) residents during 25 minute sessions. Eight different stem questions were scheduled in a pattern so as to eliminate prior trainee knowledge of the exam content. However, despite differences in stem questions themes, each was identically structured into preoperative, intraoperative and postoperative question subsets to ensure maximum uniformity. Each examiner independently graded the trainee by assigning an overall score (70,73,77 or 80; pass = >75), a subscore of 1-4 for each subset question and by marking deficiencies in clarity (C), judgement (J), application of knowledge (AK) and adaptability (AD) for each subset question. The exam concluded with a debriefing period conducted by examiners to point out deficiencies and offer advice to examinees, who subsequently evaluated the OPE experience by questionnaire. Written tests results included in the analysis were the standard scores from the AKT-6, the ITE one year prior to OPE and the percent-correct scores of semiannual DEs. Indicators of clinical competence included the cumulative z-scores of negative faculty comments regarding knowledge (KNW), patient management skills (MG) and total clinical compentency score (TOT) derived from DRPEC. The data were analyzed using t-tests, ANOVA and correlation coefficients where appropriate.

Results: Mean total scores, mean subset scores and the frequency of C, J, AK, AD and total deficiencies were not different among the CA2, CA3 and CA4 groups, with the exception of significantly worse performance of CA4 trainees in the postoperative question subset. However, 3/10 CA2, 7/11 CA3 and 0/3 CA4 trainees were considered to have passed the OPE. Mean preoperative and intraoperative question subset scores as well as J, AK, AD and total deficiencies were strongly ($P \leq 0.001$) correlated with overall scores. Among the indicators of resident performance, only the results of the ITE and DE taken one year prior to the OPE (unadjusted for level of training but at least 6 months after the start of the clinical anesthesia [CA] years) correlated significantly with OPE pass rate, overall mean score, mean intraoperative subset score and frequency of J deficiency ($p<0.001$). Interestingly, when written test scores were adjusted for level of training (by examining only tests administered 18 months after the start of CA) no correlation with overall or component OPE scores was apparent (see Table 1). A pattern of weak but consistently evident associations ($0.01>P>0.05$) between clinical competency z-scores (see Table 2) and OPE results (i.e. pass rate, mean overall and subset scores as well as frequency of AK) was apparent.

Discussion: The correlation between written exam scores (ITE 7/88, DE 6/88) and overall OPE score is likely due to the fact that neither test accounted for different levels of training. More advanced residents, therefore, did better both on written and oral exams. Since the correlation disappears when written exam scores from equivalent training points (e.g. DE at 18 months) are inspected, our OPE may indeed test for qualities which are different from those assessed by written examinations. An alternate explanation might be that, as level of training progresses, the acquisition of knowledge (as tested by written exams) becomes a necessary but perhaps not sufficient prerequisite for success in an oral examination. We had expected a better correlation between OPE scores and clinical compentence KNW and, particularly, MG and TOT scores. We believe the observed weak correlations are most likely a result of our, as yet, small sample size. Alternatively, it is possible that the OPE tests a different aspect of clinical compentence than do daily faculty assessments of resident performance. Insufficient homogeneity within our OPE may also have prevented the demonstration of a stronger association. However, the latter is less likely in view of the excellent internal correlation between OPE overall score (or pass rate) and virtually all component subset and deficiency scores. Further work is in progress to clarify these issues.

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Table 1: Written Test Results and Overall OPE Score

	n	Rho	p
AKT-6	14	0.063	n.s.
ITE 7/38	17	0.639	<0.01
DE 6/88	17	0.684	<0.01
DE 18 mo	17	0.014	n.s.

Table 2: Correlation Coefficients For OPE vs. Clinical Competence Scores

	Overall	Preop	Intraop	Postop
KNW	0.43*	0.35	0.47*	0.61#
MG	0.52*	0.59#	0.50*	0.50*
TOT	0.39	0.33	0.44*	0.53*

*P<0.05 #p<0.01

FENTANYL DOES NOT EFFECT THE SPECTRAL EDGE FREQUENCY IN HUMAN NEONATES

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Introduction:

The electroencephalogram has been used in the operating room as a monitor of brain function since 1950. Until recently it was difficult to display this complex signal in a concise form. Numerous methods of automated EEG processing are now available which have made intraoperative EEG monitoring clinically useful. The spectral edge frequency (SEF) is one such descriptor of EEG activity. It reflects the highest frequency present in the EEG and has been used as a gauge of anesthetic depth[1]. In adults, narcotic anesthetics cause the spectral edge to shift from higher to lower frequencies[2]. We sought to determine the effect of fentanyl on the spectral edge frequency in term newborn infants.

Methods.

After obtaining approval from the Human Subjects Committee, six unpremedicated ASA physical status I or II term infants less than three months old were studied. Written informed consent was obtained from the parents of all infants. An intravenous line was started prior to the induction of anesthesia. The skin of each patient was prepared with Omni Prep^R (D.O. Weaver, Denver, CO). Standard scalp EEG was recorded using EEG adhesive disk electrodes placed bilaterally in a frontal ipsilateral mastoid configuration. Electrode placement was adjusted until impedances were all below 5,000 ohms. The signals were analyzed by a Neurotrac^R (Interspect, Conshohocken, PA) monitor. Data were displayed in the compressed spectral array format. The data were updated every 16 seconds and overlaid with the calculated spectral edge frequency. Baseline recordings were made prior to induction. Anesthesia was then induced with fentanyl 2.5 μg/kg followed by atropine .01 mg/kg and vecuronium 0.1 mg/kg. The infants were ventilated with 100% O_2 by face mask to normal end-tidal CO_2 for 5 minutes after administration of fentanyl. Spectral edge frequency was measured at 1 minute intervals following the administration of fentanyl and compared to baseline values prior to induction of anesthesia. The data were analyzed using a repeated measures analysis of variance.

Results.

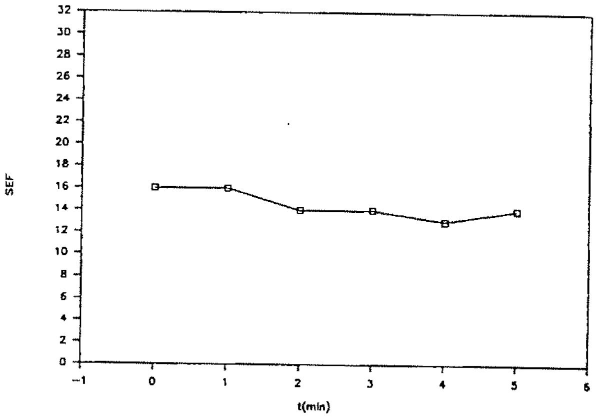
The data on all six infants is displayed in Figure 1. Fentanyl did not significantly cause a shift in the spectral edge frequency in any of the six infants studied. There were no significant intra-hemispheric differences noted. Four out of the six patients showed a trend towards lower frequencies. Two out of the six actually showed an increase in the spectral edge frequency following administration of fentanyl.

Discussion.

This is the first report of the effect of fentanyl on the processed EEG in term newborns. Anesthesiologists caring for infants have long sought a non-invasive gauge of narcotic effect. We wanted to determine if the spectral edge frequency could be used as an end point for narcotic administration in babies. There are several possible reasons why fentanyl did not produce a shift in the spectral edge frequency in this study: 1) In term newborns the baseline EEG activity is slower than in adults. Thus the change due to drug administration will be smaller. 2) The dose of fentanyl was low. Higher doses maybe needed to effect a change in the electroencephalogram. 3) These patients were studied for only five minutes after fentanyl was given. Stanski[3] has shown that changes in the spectral edge following fentanyl administration in adults correlate with serum fentanyl levels but lag behind by approximately seven minutes. It may be that fentanyl penetration into the CNS in term infants takes longer than adults.

There has been much attention lately on analgesia for pediatric patients. Further work is needed to answer the question of how much narcotic is enough and whether the processed EEG will be a useful tool for monitoring narcotic effect in infants.

Figure 1



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Title: NIMODIPINE DECREASES THE MINIMUM ALVEOLAR CONCENTRATION OF ISOFLURANE IN DOGS

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Introduction. Previous investigators have reported a reduction in anesthetic requirement with administration of drugs that act on calcium channels (1,2). Nimodipine is a calcium channel antagonist that has gained popularity in the treatment of patients undergoing surgery for intracranial aneurysms (3). The present study was undertaken to determine the effect of nimodipine on the minimum alveolar concentration (MAC) of isoflurane in dogs.

Methods. This study was approved by the Institutional Committee on Research Involving Animal Subjects. General anesthesia was induced by inhalation of isoflurane 2-3% and oxygen via mask in 6 mongrel dogs weighing 15-19 kg. Tracheal intubation was accomplished with a cuffed 8.0 mm endotracheal tube without the use of muscle relaxants. The dog's lungs were then ventilated at a rate of 10 breaths per minute. The tidal volume was adjusted to achieve an end-tidal carbon dioxide tension between 28 and 38 mmHg, as measured by infrared analysis (Siemens). Catheters were inserted into a femoral vein and artery and a continuous iv infusion of lactated Ringer's solution was begun at the rate of 4 ml/kg/hr. A heating pad was used to keep nasal temperature at 37.0 ± 0.5° C. Temperature, ECG, arterial blood pressure and end-tidal carbon dioxide tension were continuously recorded. Isoflurane concentration was measured by infrared analysis with a Puritan Bennet Anesthetic Agent Monitor 222. The analyzer was calibrated for each study. Exhaled gas was obtained from a 5-1/4 inch 16 gauge Teflon catheter inserted through the endotracheal tube.

The MAC of isoflurane necessary to prevent purposeful movement in response to tail clamping was determined according to the method of Eger et al (4). The base of the tail was shaved. After a stable end-tidal isoflurane concentration was maintained for at least 15 min a clamp was applied to the base of the tail and closed to full ratchet lock for 1 min or until purposeful movement was elicited. Following the determination of the response to the tail-clamp, the end-tidal isoflurane concentration was adjusted either up or down as appropriate, and the response to tail-clamp was again determined. MAC was determined to be midway between the stable end-tidal concentrations of isoflurane (to the nearest 0.1 volume percent) at which the animal did or did not move in response to the stimulus.

Following the determination of the control MAC for isoflurane, each dog received a continuous iv infusion of nimodipine at a rate of 0.5 µg/kg/min. After 30 min of infusion, MAC was again determined by the same technique. MAC determinations were repeated after 30 min of nimodipine infusion given at an increased rate of 1.0 µg/kg/min and finally after 30 min of 2.0 µg/kg/min infusion.

Control values for MAC, obtained before infusion of nimodipine, and at each drug infusion rate were compared by repeated measures one-way analysis of variance. $P<0.05$ was considered statistically significant.

Results. As shown in the table, the MAC of isoflurane decreased following the administration of nimodipine. There were no significant differences in the magnitude of MAC reduction among the three doses of drug. The mean reduction in MAC was 19.5 percent of the control value.

Discussion. Altered neuronal fluxes of calcium are considered to play an important role in the mechanism of general anesthesia. Such neuronal functions as neurotransmitter release, postsynaptic transmission and metabolism of intracellular messengers are all mediated by calcium ions. Calcium channel antagonists have been reported to increase the potency of a variety of drugs, including ethanol, nitrous oxide, barbiturates, benzodiazepines, and volatile anesthetics (1,2).

Our results indicate that the calcium channel antagonist, nimodipine, potentiates the anesthetic action of isoflurane. In clinical practice, isoflurane dosages may need to be reduced in patients receiving concurrent nimodipine therapy.

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Table. MAC OF ISOFLURANE BEFORE AND AFTER NIMODIPINE (n = 6) (Mean ± SD)

	MAC
Control	1.47 ± .325*
Nimodipine (0.5 µg/kg/min)	1.19 ± .182
Nimodipine (1.0 µg/kg/min)	1.15 ± .179
Nimodipine (2.0 µg/kg/min)	1.15 ± .089

*P < 0.05 compared to MAC after nimodipine.

TITLE: COMPUTER-CONTROLLED INFUSION OF SUFENTANIL FOR CARDIAC SURGERY

AUTHORS: I. M. SCHWIEGER, M.D., J. M. BAILEY, M.D., Ph.D., AND C. C. KUG, Jr., M.D., Ph.D.

AFFILIATION: Departments of Anesthesiology, Emory School of Medicine (Division of Cardiothoracic Anesthesia), Atlanta, Georgia and University Hospital, Geneva, Switzerland.

INTRODUCTION:

Because sufentanil (S) equilibrates rapidly across membranes, it is assumed that its plasma concentrations ([S]) reflect those at its sites of action in the CNS. Clinically useful [S] range from those inducing unconsciousness in the premedicated, unstimulated patient to those required to abolish responses to noxious stimuli (i.e., therapeutic window ([TW])).[1] Computer-controlled infusion techniques allow [S] to be varied rapidly in a proportional manner which facilitates definition of [S] vs effect relationship. We determined the TW of [S] in patients undergoing coronary artery bypass grafting (CABG).

METHODS:

After institutional approval, 6 male and 3 female hemodynamically stable patients weighing 79±17 kg, and scheduled for CABG consented to the study. Midazolam 0.1 mg/kg was injected im 1 h before anesthesia was induced by a S infusion controlled by a computer programmed to produce a predetermined target [S]. After loss of consciousness (LOC), S was varied in order to determine the lowest [S] necessary to suppress responses to noxious stimulation. Tracheal intubation was facilitated with succinylcholine 1.5 mg/kg. Thereafter a normal train-of-four was maintained until the initiation of cardiopulmonary bypass when the study was completed. The presence or absence of somatic (bodily movement, swallowing, grimacing), hemodynamic (increases in heart rate > 15 bpm, and mean arterial pressure > 15 mmHg) and sympathetic (tearing, sweating) responses to noxious stimulations were noted at tracheal intubation (1), skin incision (2), and sternotomy (3), and were correlated with [S]. In the absence of response to stimulation, [S] was decreased by 50% every 3 min until a response occurred. In the presence of a response, the [S] was increased by 50 % until the response was controlled. [S] was determined by radioimmunoassay. Statistical analysis included one-way analysis of variance and linear regression as required. P<0.05 was considered significant. All results are expressed as mean±SD.

RESULTS:

LOC occurred in 9/9 patients with a [S] of 17±8 ng/ml 5±3 min after initiation of the S infusion. The [S] required to induce LOC in 50% of patients (Cp50) was 14 ng/ml and in 95% of patients (Cp95) was 27ng/ml. The S ED50 was 2.80 ug/kg and the extrapolated ED95 was 4.02 ug/kg (Fig 1, r=0.92, p>0.01). The computer controlled infusion produced [S] at events 1, 2, and 3 of 16±6 ng/ml, 20±8 ng/ml, and 25±20 ng/ml respectively. The [S] of each response or absence of response to the 3 events are represented in figure 2 (n=27). Responses were observed in 4, 2, and 1 patient at events 1, 2, and 3 respectively. The S Cp50 was 20 ng/ml for all 3 events (Fig 2).

DISCUSSION:

Both the ED50 and the ED95 for S found in this study confirmed previous results.(2) Though there was no significant difference in the mean [S] at all 3 events, the S concentration required to suppress responses to noxious stimulation ranged from 13-28 ng/ml at intubation, 9-37 ng/ml at skin incision, and 8-69 ng/ml at sternotomy. This defines the range of [S] that are likely to be useful (TW) and represent the variability among patients undergoing CABG.(3) The wide variability in anesthetic dosage indicates the necessity of tailoring dosage to the individual patient in order to use anesthetic drugs effectively and allow an appropriately rapid recovery.

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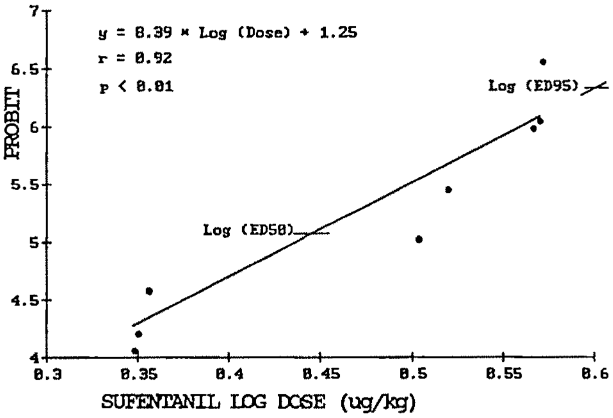

FIGURE 1: Regression analysis of sufentanil (log dose vs probit) for loss of consciousness in all 9 patients. All patients received midazolam as premedication (0.1 mg/kg IM) 1 hour before induction of anesthesia with the S infusion.

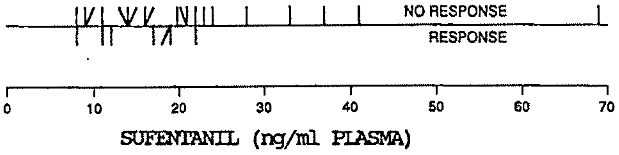

FIGURE 2: Relationship between the sufentanil plasma concentrations and their effects for 3 specific events of short duration (intubation, incision, sternotomy). This diagram shows the sufentanil concentration of every patient associated with (downward deflection) or without (upward deflection) a response to each of the 3 stimuli.

TITLE: EVALUATION OF A COMPUTER-CONTROLLED INFUSION OF SUFENTANIL FOR CARDIAC SURGERY

AUTHORS: I. M. SCHWIEGER, M.D., J. M. BAILEY, M.D., Ph.D., AND C. C. HUG, Jr., M.D., Ph.D.

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INTRODUCTION: Computer assisted continuous infusion devices have been developed to rapidly achieve and maintain predetermined constant plasma concentrations of intravenous anesthetics. Programs are available which accept a specific plasma concentration input and employ a pharmacokinetic model to produce the infusion scheme needed to achieve the desired concentration.(1) A program for sufentanil (S) has been developed for cardiac surgery but not as yet evaluated. The purpose of this study was to evaluate this program for use in producing and maintaining sufentanil anesthesia in patients undergoing aortocoronary bypass surgery (CABG).

METHODS: After obtaining institutional approval and informed consent, 9 preoperatively hemodynamically stable patients presenting for elective CABG entered into the study. Premedication included midazolam 0.1 mg/kg IM 1 hour before induction of anesthesia. This was obtained by an infusion of sufentanil via an IMED 929 pump under the control of a Compaq 386 computer using the program developed by Shafer et al. (personal communication) which included the pharmacokinetic parameters of Bovill et al.(2) The S infusion was programmed to achieve specific plasma concentrations of sufentanil ([S]). This variable S infusion was used and titrated to maintain stable hemodynamics (mean blood pressure within 15 mmHg of normal and heart rate within 15 beats/min of normal) and to prevent or suppress somatic responses to intubation, incision, sternotomy, and multiple episodes of electrocauterization in the mediastinum. Blood was sampled at the time of each stimulus and after any change in the target S concentration. The [S] was determined by radioimmunoassay. Data were analyzed by linear regression.

RESULTS: Using the computer controlled infusion of S we were able to maintain stable hemodynamics and suppress somatic responses to noxious stimulation albeit at the expense of very high [S] (> 20 ng/ml in 8, > 30 ng/ml in 5, >40 ng/ml in 3, and > 60 ng/ml in 1 patient). These, however, did not modify the postoperative care in the intensive care unit, or delay extubation in 8/9 patients. One patient required prolonged postoperative ventilation due to slow awakening. The relationship between the target [S] and the actual measured [S] is shown in the figure. It can be seen that in general the computer controlled infusion produced actual [S] in excess of the target [S]. This impression is confirmed by the absence of difference between the predictive error (i.e., the difference between the target [S] and the actual [S] expressed as a percentage of the actual [S]) and the absolute predictive error (defined as the above but using absolute values). This is consistent with a systematic overshoot of the target [S].

DISCUSSION: We have determined the accuracy of a computer controlled system for the infusion of sufentanil during cardiac surgery. We have found a good correlation between the actual plasma levels and the target concentration, although the computer controlled infusion did overshoot the target concentration. This error was consistent and did not interfere with use of the system varying the sufentanil concentrations in anticipation of different levels of stimulation. We were able to use this computer-controlled infusion to rapidly establish the sufentanil concentration necessary for maintenance of stable hemodynamics in the face of stimuli of varying intensity.

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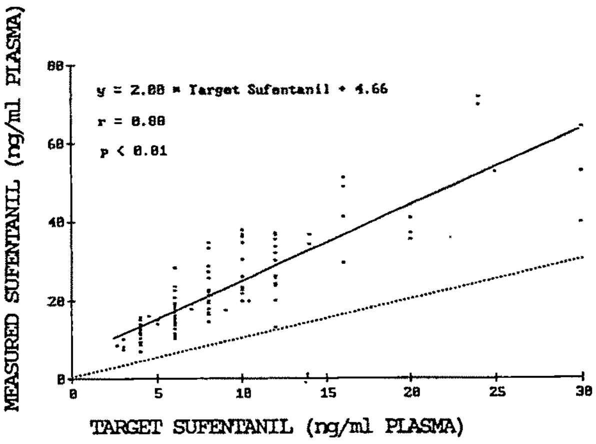

FIGURE: Correlation (——) of target and measured sufentanil plasma concentration.
(Line of identity: - - -)

TABLE: Predictive and absolute predictive errors.

Patient	1	2	3	4	5	6	7	8	9	mean±SD
Predictive error (%)	20	10	7	8	12	16	10	23	8	13±6
Absolute predictive error (%)	20	10	7	8	12	16	10	23	8	13±6

TITLE: MOLECULAR CLONING AND EXPRESSION OF A NEW ALPHA-1-ADRENERGIC RECEPTOR SUBTYPE

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INTRODUCTION

Control of vascular tone and myocardial contractility by the adrenergic nervous system is important in anesthesia and surgery. In order to understand how anesthetics interact with adrenergic receptors (ARs) and to develop pharmacologic agents which interact with ARs more specifically, it is important to define AR subtypes. Heterogeneity of alpha-2-ARs has recently been demonstrated by the cloning of two distinct subtypes,[1,2] and pharmacologic evidence for a third. Evidence also exists for heterogeneity of alpha-1 ARs.[3] We recently cloned the gene which encodes the alpha-1B-adrenergic receptor in hamster[4]; we now present the cloning of a new alpha-1-AR subtype.

METHODS

As general background, the primary structure of every cell membrane protein, such as a receptor, is encoded by DNA. Each amino acid (aa) in the receptor protein is represented by a triplet of nucleic acids in DNA. Therefore finding the DNA sequence, or gene, that codes for a receptor protein allows the primary structure of the receptor to be deduced. By introducing this gene into COS-7 expression cells, high quantities of receptor protein are made by the cell, allowing pharmacologic testing of the receptor.

Since adrenergic receptor subtypes should be similar in overall structure, a small portion of the gene (oligonucleotide) for the alpha-1B-AR was radiolabeled and used to search for a similar gene from a bovine brain cDNA library (DNA source). The double helix structure of DNA (two complementary strands of nucleic acids) allows one strand to be used as a probe, since complementary DNA strands will bind to it. In this manner, we isolated a complete "clone" or gene which encodes a new adrenergic receptor protein.

RESULTS

A single complete 3.1-kb clone was isolated under high stringency conditions. This gene contained a 1.4-kb open reading frame which coded for a 466 aa polypeptide. Hydropathicity analysis revealed seven hydrophobic regions separated by hydrophilic residues suggesting that this receptor has seven membrane- spanning regions as has been seen in other G-protein coupled receptors. This new bovine alpha-1-AR is present on a different human chromosome than the hamster alpha-1-AR, ruling out the possibility of these results being the result of species difference.

Comparison of the aa sequence in the transmembrane spanning regions revealed striking homology (identity) with the alpha-1B-AR (72%, Table 1), as compared with 42% homology with other adrenergic receptors. 72% transmembrane homology is compatible with AR sub-subtypes, as was seen with the alpha-2-ARs.[2] Expression of the clone in COS-7 cells and binding with the specific alpha-1-antagonist [125I]HEAT confirms alpha-1-AR binding properties.

DISCUSSION

We have cloned the gene that encodes a new alpha-1-AR subtype. The primary structure of the encoded receptor is highly homologous to the hamster alpha-1-AR and has overall structural similarity to other ARs and G-protein coupled receptors. Further pharmacologic and biochemical characterization of this receptor will be required to determine if this receptor is the alpha-1A-AR described in the literature,[3] or another subtype. The discovery of new adrenergic receptor subtypes is important in many aspects of anesthesia and medicine. With such information, more specific pharmacologic agents for AR subtypes can be developed, free from side-effects caused by nonspecific AR binding. This may ultimately allow us to study the interaction of anesthetics and the adrenergic nervous system at a molecular level.

TABLE 1 -- TRANSMEMBRANE AMINO ACID HOMOLOGY OF THE NEW ALPHA-1-ADRENERGIC RECEPTOR WITH OTHER ADRENERGIC RECEPTORS

Receptor	% Transmembrane Homology
Hamster alpha-1B-AR	72.1%
Human beta-2-AR	42.1%
Human beta-1-AR	43.2%
Human alpha-2-C10-AR	41.5%
Human alpha-2-C4-AR	43.2%

Note: Interspecies overall homology ranges 87-99%; interspecies transmembrane homology is even higher. Therefore these differences are due to receptor subtypes, and not to the species listed.

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*Dr. Schwinn is the ASA/AUA 1988 Research Fellow. This work is supported by the ASA/AUA Research Award.

Title: PHARMACOKINETICS OF VECURONIUM AFTER LONG-TERM ADMINISTRATION

Authors: V Segredo, M.D., JE Caldwell, M.D., MA Matthay, M.D., ML Sharma, Ph.D., LD Gruenke, Ph.D., RD Miller, M.D.
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Introduction. Vecuronium is commonly used in the intensive care unit because it is free of cardiovascular effects, and its duration of action is little affected by kidney or liver disease. In this situation may be administerd to patients continuously for many days. At present nothing is known about the pharmacology of administering vecuronium for such a prolonged period. Our purpose in this study was to define the pharmacokinetcs of vecuronium in patients in the intensive care unit at two time points; following the initial dose of vecuronium; after patients had been receiving vecuronium for several days.

Methods. After approval by our Committee on human Research, and obtaining written consent, we studied 9 critically ill patients who required neuromuscular blockade to facilitate mechanical ventilation. In the 5 patients, who were receiving a neuromuscular blocking drug for the first time, vecuronium, 0.03-0.1 mg/kg, was infused iv over 10 min. Venous blood samples were drawn every 2 min during the infusion and at increasing intervals for the next 360 min. Vecuronium plasma concentrations were measured by gas chromatography assay .[1] Plasma concentration *vs* time data were fit to a two compartment model by derivative-free non linear regression. Plasma clearance, volume of distribution (Vd$_{area}$), and elimination half-life were calculated from standard formulae.[2] The remaining four patients had all been receiving vecuronium, as intermittent bolus injections, for at least three days. In these patients no longer required neuromuscular blockade the mode of administration of vecuronium was changed from bolus to infusion. To ensure steady state conditions, the infusion rate was adjusted to maintain a stable level of neuromuscular blockade (train-of-four ratio = 10%). When neuromuscular responses and infusion rate had been stable for at lkeast 45 min, the infusion was stopped. Vecuronium plasma clearance was calculated by dividing the infusion rate by the steady-state plasma concentration, elimination half-life was calculated by linear regression of the log plasma concentration *vs* time data following cessation of the vecuronium infusion, and volume of distribution calculated from clearance and elimination half-life.[2] Pharmacokinetic parameter for the patients in the two groups were compared by Student's t test; $P < 0.05$ was considered significant.

Results. Of the 5 patients given vecuronium for the first time, 2 had combined renal and liver failure, 2 had liver failure alone and one had renal failure alone. Of the 4 who had received vecuronium for several days, one had liver failure and one had liver failure. The volume of distribution and elimination half-life of vecuronium were increased in the patients who had received vecuronium for several days, compared to those who were receiving their first dose. Plasma clearance was not different between the two groups.

PHARMACOKINETIC VARIABLES: Individual results and means ± SD

	Plasma Clearance (ml/kg/min)	*Vd$_{area}$ (l/kg)	*Elimination half-life (min)
Patients receiving first dose of vecuronium			
1	3.6	0.41	79
2	3.1	0.33	73
3	2.2	0.24	73
4	3.0	0.25	58
5	3.9	0.20	34
	3.2 ± 0.6	0.29 ± 0.09	63 ± 18
Patients receiving vecuronium for several days			
1	2.8	0.50	130
2	3.1	0.90	336
3	2.2	0.60	147
4	3.0	0.40	192
	2.3 ± 0.7	0.60 ± 0.20	210 ± 93

* $P < 0.05$ between patient groups

Discussion. In the patients who were receiving their first dose of vecuronium our values for clearance, volume of distribution and elimination half-life are similar to those reported by Lynam et al. for patients with renal failure.[4] The reason for the increased elimination half-life in the group who received vecuronium for several days is due to the increased volume of distribution. Our value is greater than any previously reported in patients with organ failure. [3,4,5]. This increased volume of distribution and prolonged elimination half-life may account for our observation of prolonged neuromuscular blockade in some patients whom have received long term adminstration of vecuronium in the intensive care unit.*

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Title: PHARMACODYNAMICSS OF VECURONIUM AFTER LONG-TERM ADMINISTRATION

Authors: V Segredo, M.D., MA Matthay, M.D., JE Caldwell, M.D., ML Sharma, Ph.D., LD Gruenke, Ph.D., RD Miller, M.D.
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Introduction. Vecuronium is widely used in critical care medicine because it lacks cardiovascular side effects, and its duration of action is only slightly affected by kidney or liver failure. However, there are some reported cases of prolonged neuromuscular blockade following long term administration of vecuronium in critically ill patients. Many factors could contribute to prolonged blockade. Vecuronium's 3-desacetylmetabolite could be one of these factors. In cats, 3-desacetylvecuronium (3-desvec) is 80% as potent as vecuronium (1,2). In humans, its elimination seems to depend on renal function (3). The objective of this study was to determine the pharmacodynamics of vecuronium and its 3-desacetylmetabolite in critically ill patients who have received vecuronium for several days.

Methods. After approval by our Committee on Human Research, and relative's written consent, 8 critically ill patients who required paralysis to improve mechanical ventilation were studied. Patients were included in the study either if they had a prolonged neuromuscular blockade after stopping vecuronium administration (> 4 h) or if they had been receiving vecuronium for at least 3 days. In patients having received vecuronium for more than 3 days, when vecuronium administration was to be discontinued, its mode of administration was changed from intermittent bolus to continuous infusion. The infusion rate was adjusted to obtain a stable level of paralysis with at the TOF stimulation a fourth twitch being 10% of the first twitch (TOF10%). After 30 min of stable neuromuscular response to the same infusion rate, 4 arterial blood samples were withdrawn at 0, 10, 15 and 20 min. In patients with prolonged blockade after termination of vecuronium administration, no infusion was performed, but only blood withdrawal and neuromuscular function monitoring . Neuromuscular blockade was monitored by measuring the force of contraction of the adductor pollicis muscle following supramaximal stimulation of the ulnar nerve at the wrist. Stimuli of 0.2 ms duration were delivered in a train-of-four sequence (2 Hz) which was repeated at intervals of 10 seconds.Vecuronium and its 3-desacetylmetabolite plasma concentrations were measured by gas chromatography assay. We don't report parent compound and metabolite concentrations separately but the sum of both concentration, 3-desvec concentration being weighted by 80% (its potency ratio in cats), postulating the same potency ratio in humans than in cats.

Results. Four of the 8 patients remained paralysed more than 4 hours after termination of vecuronium administration (no twitch at the TOF stimulation of the ulnar nerve at the wrist). Two died without recovering a twitch (patients 1 and 2). For the two other patients we report the lower muscle relaxant concentration sum before full recovery of neuromuscular function. It should be noticed that all these patients had poor renal function (creatinin clearance <20 ml/min), whereas the patients not having prolonged neuromuscular blockade after vecuronium discontinuation had a creatinine clearance of at least 20 ml/min. The presence of prolonged paralysis doesn't seem to be related to liver dysfunction, to total vecuronium dose received, to duration of treatment, or to any medication received. In the 4 remaining patients in whom a steady state could be performed, we determined the muscle relaxant concentration sum (CpssTOF10%) associated with a stable TOF=10%. This CpssTOF10% appears to be very variable and in half of the patients it is higher than the Cpss90 (vecuronium concentration at steady state giving a 90% depression of control twitch tension) for healthy patients (165±48 ng/ml)(4).

Discussion. Because of the many potentiators of neuromuscular blockade existing in ICU patients, we would have expected to find lower concentration sums. This result doesn't seem to be explained by an overestimation of 3-desvec potency in humans, because in patient #5 vecuronium concentration was high (289 ng/ml). A secondary tolerance of the neuromuscular junction to the muscle relaxant after long term exposure could explain this observation.

Patient	Group	Conc.sum (ng/ml	Effect	Creat. Cl (ng/ml)
1	paralysed >7d		0	3 ml/min
2	paralysed >8h		0	20 ml/min
3	paralysed 24h	246	T3@TOF	3.5 ml/min
4	paralysed 17h	124	T4@TOF	5 ml/min
5	liver failure	381	TOF=10%	Nal
6		96	TOF=10%	Nal
7		430	TOF=10%	20 ml/min
8		172	TOF=10%	Nal

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TITLE: THERMOREGULATORY VASOCONSTRICTION SIGNIFICANTLY DECREASES HEAT LOSS TO THE ENVIRONMENT

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Introduction. Thermoregulatory vasoconstriction decreases blood flow in cutaneous arterio-venous shunts and capillaries.[1] Decreased shunt flow changes temperature in only a small fraction of the skin surface (hands, feet, ears, lips, and nose),[1] while capillary constriction may affect temperature throughout the body. Thus, total cutaneous heat loss during exposure to cold cannot be deduced from fluctuations in central temperature alone because central temperature is altered by redistribution of body heat as well as other factors (shivering, nonshivering thermogenesis). Therefore, we directly measured heat flux across the skin to determine the distribution of cutaneous heat loss during cold exposure and the extent to which thermoregulatory vasoconstriction decreases loss.

Methods. With approval of our Committee on Human Research and written consent, we studied five volunteers exposed to a 28°C environment. We measured heat loss from ten skin-surface sites in watts/M^2 using thermal flux transducers (Thermonetics, San Diego, California). These values were converted into watts/site by multiplying by the calculated body surface area of each volunteer and assigning the following regional percentages: head—6%, upper arms—9%, forearms—6%, palms—2.5%, fingers—2%, back—19%, chest and abdomen—19%, thigh—19%, calves—11.5%, feet—6.%. (The basal metabolic rate in adult humans is ≈ 70 Watts.) Tympanic membrane and ten skin-surface temperatures were monitored using Mon-a-Therm® (St. Louis, Missouri) thermocouple probes. Control measurements were taken over a 10 min period. Thermoregulatory vasoconstriction was then induced by intravenous administration of 4 L Ringer's solution cooled to 4°C, and heat flux and temperature measurements repeated. Significant vasoconstriction was prospectively defined as a skin-surface temperature gradient (finger tip temperature - forearm temperature) ≥ 4°C.[2]

Results. The distribution of heat loss before and after vasoconstriction appears in the table (individual measurement sites were pooled into major anatomic areas). Approximately 65% of the total heat flux crossed the arms and legs, while only ≈ 16% emanated from the back and head. Vasoconstriction decreased total heat loss 13 ± 5.1% (mean ± SD; 8.8 ± 3.5 watts) (Fig.) and flux across the hands by 51 ± 16% (1.6 ± 0.6 watts).

Discussion. Most metabolic heat was lost across the arms and legs; losses from the head and back were small. Thermoregulatory vasoconstriction significantly decreased cutaneous heat loss; the largest fractional decrease occurred in skin known to have arterio-venous shunts.

Heat Flux During Vasoconstriction

	Total	Arms	Hands	Head
Control (watts)	70±3.9	20±4	3.1±1.1	7.0±1.4
% of Total Flux	100	29±4.9	4.5±1.4	9.9±1.8
Vasoconstriction (watts)	61±5.3	15±4.0	1.6±0.8	6.3±1.3
Change (watts)	8.8±3.5	5.1±3.0	1.6±0.6	0.7±0.1
% Change	-13±5.1	-25±15	-51±16	-9.9±0.7
P≤0.05	*	*	*	*

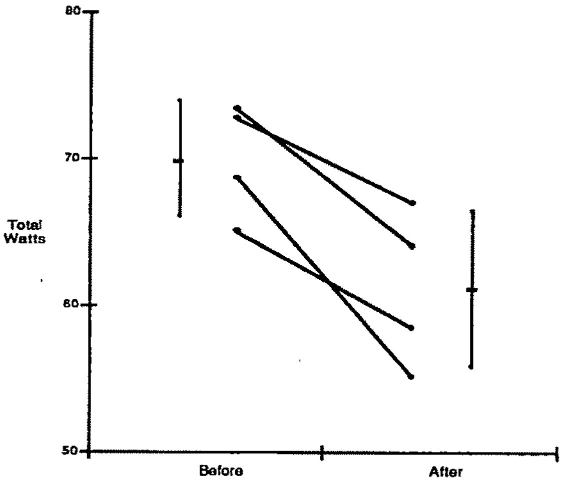

Fig. Thermoregulatory vasoconstriction decreased total cutaneous heat flux 13% ($P = 0.02$). Each line represents total heat loss in one volunteer before and after significant vasoconstriction. The mean flux (watts ± SD) before and after vasoconstriction appear on the far left and right sides of the figure, respectively.

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Supported by NIH grant #R29 GM39723.

TITLE: VALIDATION OF SKIN-SURFACE TEMPERATURE GRADIENTS AS MEASURES OF CENTRALLY-MEDIATED PERIPHERAL VASOCONSTRICTION

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Introduction. Forearm - fingertip skin-surface temperature gradients have been used as an index of intraoperative thermoregulatory vasoconstriction.[1,2] (A gradient ≥ 4°C indicates significant constriction.) This gradient correlates well with cutaneous perfusion determined using laser Doppler flowmetry,[2] but has not been compared with heat loss, which is the physiologically significant parameter. Therefore, we tested whether forearm - fingertip gradients correlate with heat loss from the fingers and with facial vasoconstriction.

Methods. With Committee on Human Research approval and written consent, we induced thermoregulatory vasoconstriction in five volunteers by IV administration of 4 L Ringer's solution cooled to 4°C. Forearm - fingertip temperature gradients (AF) were compared with a new skin-surface temperature gradient (forehead - nose temperature, HN) and with heat loss from the finger. Heat loss was measured using a thermal flux transducer (Thermonetics, San Diego, California). Central (tympanic membrane) and skin-surface temperatures were monitored using Mon-a-Therm® (St. Louis, Missouri) thermocouple probes.

Results. Forearm - fingertip skin-surface temperature gradients correlated well with heat flux from the fingers: **Flux = 37.7 - 6.2*(Gradient)**, *r* = 0.84, n=184 (Fig. 1). Forearm - fingertip skin-surface temperature gradients (AF) correlated well with the new forehead - nose gradients (HN): **HN = AF*0.6 + 0.68**, *r* = 0.89, n = 184 (Fig. 2). Thus, an arm gradient of 4°C corresponded to a forehead - nose gradient of 3°C.

Discussion. The correlation we observed between blood flow (*i.e.*, arm skin-temperature gradients) and heat loss from the fingers suggests that both may be used to evaluate cutaneous thermoregulatory function. However, determination of actual heat loss still requires direct measurements because the relation between the gradient and flux is strongly dependent on ambient temperature, air flow, skin covering, and other factors. During epidural anesthesia, measurements of peripheral cutaneous perfusion are not useful indicators of centrally mediated vasoconstriction, because anesthesia-induced sympathetic blockade frequently prevents vasoconstriction in the arms and legs. However, sympathetic innervation of the nose is mediated by a direct cephalic prolongation of the superior cervical ganglion, the internal carotid nerve. The preganglionic nerves supplying the superior cervical ganglion arise from C8 through T2 (and are relatively resistant to blockade by local anesthetics).[3,4] It is therefore likely that forehead - nose gradients reliably reflect thermoregulatory vasoconstriction mediated by the hypothalamus when sympathetic blockade extends below T2, as is common during epidural anesthesia.

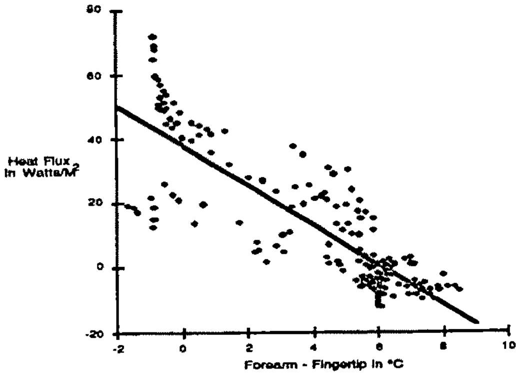

Fig. 1. Mean heat flux in watts/M^2 from the fingers correlated well with forearm - fingertip skin-surface temperature gradients: **Flux = 37.7 - 6.2*(Gradient)**, *r* = 0.84, n=184. Negative flux (heat absorbed from the environment) occurred when drafts transiently produced local ambient temperature greater than fingertip temperature.

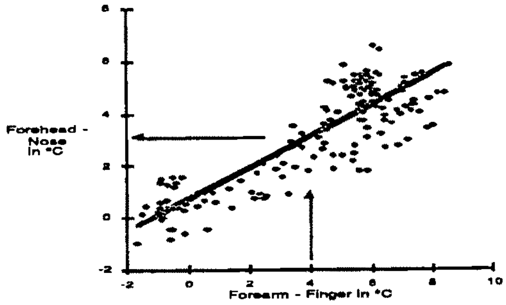

Fig. 2. Forearm - fingertip skin-surface temperature gradients (AF) correlated well with the new forehead - nose gradients (HN): **HN = AF*0.6 + 0.68**, *r* = 0.89, n = 184. The arrows indicate that a significant forearm - fingertip gradient (prospectively defined as ≥ 4°C) corresponds to a forehead - nose gradient ≥ 3°C

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Supported by NIH grant #R29 GM39723 and Mon-a-Therm, Inc.

Title: **Facial Nerve TOF Stimulation May Not Indicate Adequate Recovery of Neuromuscular Function**
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ntroduction: Accurate measurement of neuromuscular junction integrity is imperative to ensure adequate recovery and prevent respiratory insufficiency secondary to residual neuromuscular blockade. Train-of-four (TOF) stimulation of the facial nerve has become a popular intra-operative monitor of neuromuscular blockade due to its accessibility and convenience. Since TOF stimulation of the hypothenar muscles indicating a T4/T1 ratio of ≥ 0.70 has been shown to be consistent with adequate respiratory function[1], the purpose of this study was therefore to compare the TOF stimulation of the hypothenar and orbicularis oris muscles in patients during general anæsthesia following vecuronium administration.

Methods: With institutional approval, eight healthy patients (ASA 1-2), aged 20-61 were studied. General anæsthesia was induced with thiopentone (3-5 mg•kg^{-1}), lidocaine (1.0 mg•kg^{-1}), fentanyl (3 μg•kg^{-1}), and tracheal intubation facilitated with succinylcholine (0.5–0.75 mg•kg^{-1}). Maintenance anæsthesia consisted of oxygen/nitrous oxide (FIO_2 0.30–0.40) to maintain $S_aO_2 \geq 96\%$, and isoflurane (0.5–1.0%). Positive pressure ventilation was used to maintain normocapnia (Nellcor capnograph). Using two Datex NMT–221 monitors (Puritan–Bennett), electromyograms (EMGs) were recorded simultaneously with surface electrodes over the hypothenar and orbicularis oris muscles in response to TOF supramaximal stimuli delivered to the ulnar and facial nerves respectively at a frequency of 2 Hz. Thirty minutes were allowed to elapse following succinylcholine administration to provide full recovery of the EMG. Then, control EMGs were recorded. Vecuronium (0.03-0.05 mg•kg^{-1}) was administered (time zero) to abolish T4. Spontaneous recovery of neuromuscular function was allowed to occur while the EMGs with display of T4/T1 ratios were continuously recorded. When the T4/T1 ratio of the orbicularis oris muscle attained 0.70, the simultaneous T4/T1 ratio of the hypothenar muscle was recorded. The recovery time (from time zero to T4/T1 ratio of 0.70) was measured in both groups. For statistical analysis, comparison of the recovery time for each muscle group was made using a paired Student's t–test, and the comparison between T4/T1 ratios of the hypothenar and orbicularis oris muscles when the latter was 0.70 was made using the Wilcoxon ranked sum test. Results are expressed as mean ± SD.

Results: The time of onset of neuromuscular blockade and the level of maximum blockade achieved was similar in both muscle groups in each patient. However, the orbicularis oris muscle group was first to recover in all cases. The time required for the orbicularis muscle to recover to a T4/T1 ratio of 0.70 was significantly less compared to the hypothenar muscle (46.6 ± 12.9 vs 60 ± 21, $p<0.01$). Similarly, when the orbicularis oris muscle T4/T1 ratio = 0.70, the mean T4/T1 ratio of the hypothenar muscle was significantly less (0.42 ± 0.17, $p<0.05$).

Discussion: This study compared the degree of neuromuscular blockade between the hypothenar and facial muscle groups during spontaneous recovery following vecuronium administration. Our results indicate that when the orbicularis oris muscle T4/T1 = 0.70, a significant depression in hypothenar muscle neuromuscular function co-existed. This level of blockade is capable of causing respiratory impairment. As well, a mean of 14 minutes elapsed before the hypothenar muscles recovered to a T4/T1 ratio = 0.70, (a level consistent with adequate neuromuscular recovery). Our findings suggest:

1. *The facial muscle groups are earlier indicators of onset of recovery of neuromuscular blockade.*
2. *The TOF stimulation of the facial muscle group may not be an accurate monitor to determine adequate recovery of neuromuscular function.*

References:

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TITLE Halothane depresses conduction of normal and accessory pathways during surgery for Wolff-Parkinson-White Syndrome

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AFFILIATION Departments of Anaesthesia, Cardiology and Cardiovascular Surgery, University Hospital, University of Western Ontario, London, Ontario, N6A 5A5.

Introduction

Several animal models have examined the effects of halothane administration on the atrio-ventricular (A-V) conduction system in intact as well as in vitro preparations. However, the effects of halothane on the electrophysiological properties of normal human A-V conduction as well as accessory (pathological) pathways has not been studied. We, therefore, present a preliminary electrophysiological (EP) study whereby we examined the influence of halothane administration on A-V conduction before surgical ablation in patients with Wolff-Parkinson-White (WPW) Syndrome.

Method

With institutional ethics approval, 4 patients with WPW Syndrome, aged 20-52, with no concomitant illnesses, were studied. The presence of an accessory pathway had been confirmed by preoperative EP studies. Patients were premedicated with lorazepam (0.06 mg•kg^{-1}, po) and morphine (0.1 mg•kg^{-1}, IM). Anesthesia was induced with sufentanil (20 µg•kg^{-1}) and vecuronium (20 mg). Positive pressure ventilation with air/O$_2$ was used to maintain normocapnia and a $S_aO_2 \geq 96\%$, (Nellcor). Other monitors included radial arterial line, CVP catheter, naso-pharyngeal temperature probe to ensure euthermia. An end-tidal halothane monitor (Puritan-Bennett) was used to ensure a steady-state administration of halothane. After sternotomy, baseline EP studies were performed using epicardial hexapolar electrodes as follows: 1) Right atrial refractory periods at cycle length 400/500 msec [including right atrial effective refractory period (RAERP), atrio-ventricular effective refractory period (AVERP), accessory pathway effective refractory period (APERP)]. Coupling intervals were in steps of 20 msec (from 300 to 400 msec) and 10 msec below 300 msec. 2) Right ventricular effective refractory period (VERP) at cycle length 400 msec. 3) Shortest cycle length (SCL) with 1:1 conduction [including normal A-V (SCL-AV) and accessory pathway (SCL-AP)]. Halothane (1.0 MAC, 0.78%) was then administered and after a steady-state was achieved, the EP protocol was repeated. For statistical analysis, comparison of EP studies before (C) and after halothane (H) administration was made using a paired Student's t-test. Results are expressed as mean ± SD.

Results

Following the administration of halothane, there was a significant depression of antegrade conduction within the accessory pathway (SCL-AP), ($p<0.05$). Similarly, in each patient, there was a consistent trend towards depression of: 1) Antegrade conduction in the normal A-V system (SCL-AV). 2) Retrograde conduction (Retro SCL-VA) and 3) an increase the effective refractory periods of the right atrium (RAERP), accessory pathway (APERP), AV node (AVERP) and right ventricle (VERP). Table 1.

Discussion

Our preliminary results showed a depression of conduction in **both** normal and accessory pathways during antegrade and retrograde conduction. Similarly, all effective refractory periods measured were prolonged. Therefore, our results suggest the use of halothane:

1) In WPW patients undergoing non-cardiac procedures, it may alter the incidence of tachyarrythmias since the incidence will become dependant upon the degree of depression by halothane of the normal versus the accessary conducting pathways.

2) However, in patients undergoing accessory pathway ablation, it may potentially conceal the pathway due to EP depression. As a result, inadequate mapping of the accessory pathway will be performed and may result in inadequate ablation.

Table 1

Antegrade Conduction: (msec)

	#Pts	Control	Halothane
SCL—AP	4	313±67	400±99*
SCL—AV	2	300±56	365±134
RAERP	4	195±21	205±29
AVERP	3	217±45	307±95
APERP	2	305±106	340±84

Retrograde Conduction: (msec)

	#Pts	Control	Halothane
SCL—VA	3	280±52	333±110
VERP	2	180±0	200±14

* $p<0.05$ mean±SD

TITLE: **THE EFFECTS OF LOW DOSE EPINEPHRINE AND PHENYLEPHRINE INFUSIONS ON THE HEMODYNAMIC RESPONSE TO EPIDURAL ANESTHESIA**

AUTHORS: Nigel E. Sharrock, MB, ChB; Robert Mineo, MS
AFFILIATION: Department of Anesthesia, Hospital For Special Surgery/Cornell Medical College, New York, NY 10021

Introduction: It is unclear what role cardiac contractility has in preservation of mean arterial pressure and cardiac index(CI) during epidural anesthesia. Reduction in CI and hypotension are frequently ascribed to reduced preload secondary to venodilatation. To examine the role of contractility on CI a controlled study comparing the hemodynamic influences of epinephrine and phenylephrine was performed wherein mean arterial pressure and preload were kept within predefined limits.

Methods: Following Institutional Review Board approval, consent was obtained from 20 patients, ages 50-80years, scheduled to undergo unilateral primary total hip replacements under epidural anesthesia. Beta blocked patients were excluded. Following epidural anesthesia, patients were randomly assigned to receive infusions of either epinephrine or phenylephrine in sufficient dose to maintain mean arterial pressure (MAP) at 55-60mmHg and pulmonary artery diastolic pressure (PAD) within 40% of pre-epidural values. All patients had diagnoses of cardiovascular, pulmonary, or renal disease warranting central monitoring. Radial and pulmonary arterial catheters were inserted under local anesthesia. ECG and pulse oximetry were monitored. All patients received supplemental oxygen at 3L/min through a nasal cannula and minimal sedation using incremental doses of midazolam 1-2mg and fentanyl 25-50mcg as needed. Fifty ml/hr of D5 1/2NS was given from the night before surgery. Patients were not fluid loaded prior the epidural anesthesia. Ringers lactate was given intraoperatively to preserve preload. Hemodynamic measurements were made with patients in the lateral decubitus position just prior to the epidural injection, every 10 minutes for 60 minutes, and at 30 minutes thereafter. Cardiac outputs were done in triplicate by thermodilution technique. Epidural anesthesia was performed at the L1-2 interspace by injecting 25 ml of plain 0.75% bupivacaine at 1 ml/sec via a 17 ga Tuohy needle. Sensory anesthetic level to T4 or above were achieved in all cases. MAP fell spontaneously in all cases and was stabilized at a 50-60mmHg by adjusting a central infusion of phenylephrine (5-50mcg/min) or epinephrine (0.5-5mcg/min). Differences in hemodynamic measurements between groups were analyzed using the Student's t Test at each time interval.

Results: Age, weight, and ASA were similar between groups. MAP fell similarly in both groups (Fig 1). CI was unchanged from baseline in the epinephrine treated group but fell significantly in the phenylephrine group (Fig 2). Stroke volume index was significantly increased at 20 and 30 minutes in the epinephrine group. Reductions in PAD were similar in each group. Heart rate(HR) was lower in the phenylephrine group (Fig 3). Systemic vascular resistence(SVR) was lower in the epinephrine group.

Discussion: Epidural anesthesia to the upper thoracic dermatomes will result in a reduction of CI. Low dose epinephrine infusions support CI and HR in a setting of low MAP and SVR. Phenylephrine, a purely alpha agent, results in significant falls in CI, HR, and SVR.

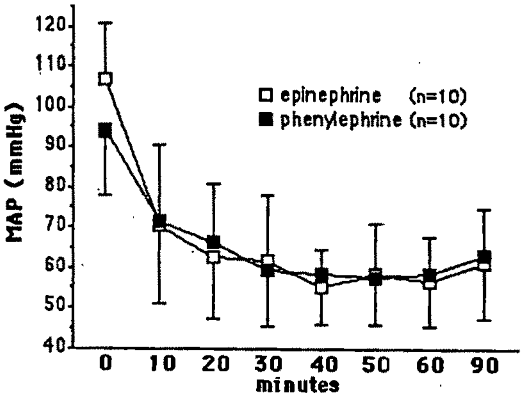

Fig 1

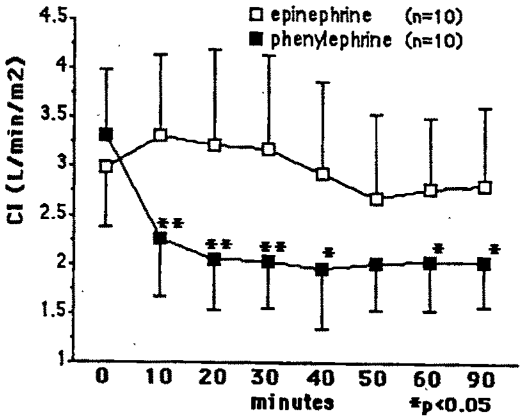

Fig 2

*p<0.05
**p<0.01

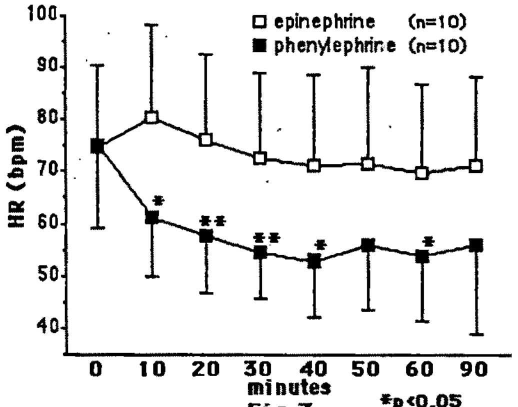

Fig 3

*p<0.05
**p<0.01

TITLE: PULMONARY HYPERTENSION FOLLOWING INSERTION OF FEMORAL PROSTHESIS DURING TOTAL HIP REPLACEMENT

AUTHORS: N.E. Sharrock, M.B., Ch. B., K.V. Sanborn, M.D., P. Castellano, R.N., R. Mineo, C.R.N.A
AFFILIATION: Department of Anesthesia, Hospital for Special Surgery/Cornell Medical College, New York, NY 10021

Introduction

Hypoxia, hypotension, and cardiac arrest have been reported in association with cemented fixation of the femoral prosthesis during total hip replacement (THR).[1] Investigation of the etiology of these phenomena have focused on methylmethacrylate monomer and bone marrow /fat embolism.[2] Bone marrow/fat embolism in this setting has been shown in dogs to produce a rise in mean pulmonary artery pressure (MPAP), and hypoxia.[2,3] It has not yet been determined whether elevations in pulmonary artery pressure and acute hypoxia occur in man in relation to cement fixation of the femoral prosthesis.

Methods

Institutional Review Board approval was obtained to prospectively study 92 patients undergoing THR (23 bilateral THR) who required pulmonary artery monitoring for medical reasons. Methylmethacrylate cement was used to fix the femoral component in 88 THR's (77%), and a non-cemented femoral prosthesis was used in 27 THR's (23%). Monitoring also included ECG, 20 ga. radial artery catheter, and pulse oximetry. Lumbar epidural anesthesia, using bupivacaine, 0.75%, produced a sensory level T1-T4 and decreased mean arterial pressure (MAP) from baseline 102 ± 18.1 mm Hg to 58.5 ± 9.5 mm Hg (mean ±S.D.) ($p<.001$). Controlled hypotension was then maintained by infusion of a vasopressor ($n=62$), sodium nitroprusside($n=6$), or both ($n=39$). Patients were lightly sedated with midazolam and fentanyl and received 3 l/m nasal O2 throughout the surgery and in the recovery room. Measurements of MAP, MPAP, and arterial blood gases were taken at baseline, during femoral reaming, before and after femoral prosthesis insertion (FPI), after reduction of the hip joint (JR) and in the recovery room (RR).

Statistical analysis was performed using ANOVA and two-group, two-tailed t-test.

Results

Figure 1 compares the changes in MPAP between cemented and non-cemented groups. There was a signiicantly greater rise in MPAP following insertion of cemented femoral prosthesis. 30 of the 31 patients (97%) who experienced Δ MPAP≥5 mm Hg were in the cemented group ($p<.005$). This rise in MPAP occurred without significant changes in heart rate (HR) or MAP and resulted in no significant decrease in paO2 acutely or in RR (Table 1).There were no significant differences in paO2 between the cemented and non-cemented groups (Figure 3).

Discussion

The cause of the rise in MPAP with insertion of cemented femoral prosthesis is not apparent but may represent 1)embolism of bone marrow, fat, cement, or air, or 2) secondary vasoactive responses in the pulmonary vasculature. These changes in MPAP do not appear to result in early hypoxia but may be a prelude to subsequent lung injury. Because our final measurements were made in the RR, we may have missed the hypoxia which can develop 24-72 hrs following lung injury due to fat embolism. We conclude that, in the setting of epidural anesthesia and controlled hypotension, 1) rise in MPAP ≥5 mmHg can occur during THR and is related to the use of cement for fixation of the femoral prosthesis; 2) patients who experience a rise in MPAP do not demonstrate changes in MAP, HR or paO2 characteristic of pulmonary fat/bonemarrow embolism.

References

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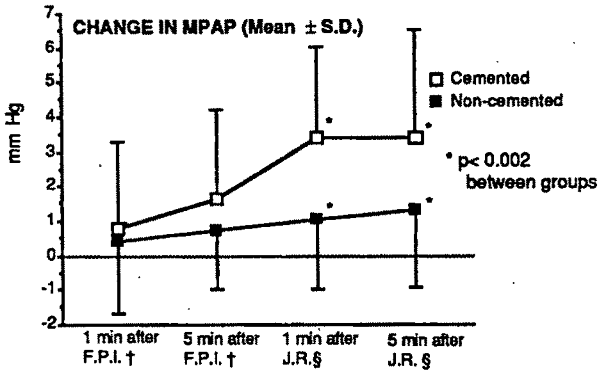


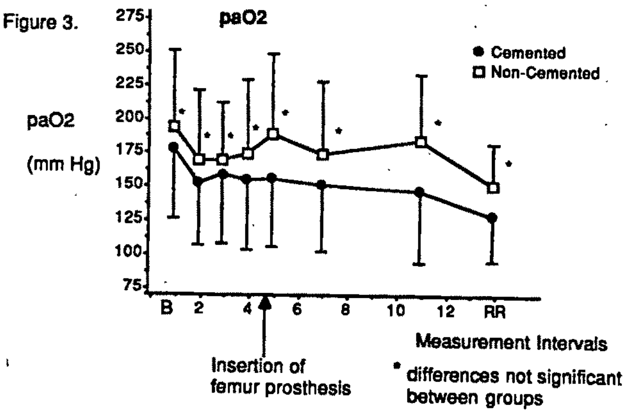
† Femoral Prosthesis Insertion
§ Joint Reduction

Table 1.

Total N = 115		↑ MPAP ≥ 5 mmHg N =31	↑ MPAP < 5 mmHg N = 84	
Cemented Femur (N)		30 (97%)	58 (69%) p<.005	
		Mean ±S.D.	Mean ±S.D.	
Δ MAP **	(mm Hg)	3.3 ± 8.6	-1.5 ± 4.7	n.s.
Δ HR **	(B/min)	0.7 ± 7.1	0.13 ± 6.8	n.s.
Δ P_aO_2 **	(mm Hg)	-11.7 ± 29.3	-4.0 ± 26.6	n.s.
Δ P_aO_2 (R.R.) #	(mm Hg)	-31.7 ± 51.4	-28.1 ± 49.8	n.s.

** Change from femoral reaming to 5 min. after Femoral Prosthesis Insertion
# Change from femoral reaming to Recovery Room Measurement

Figure 3.



TITLE: ACUTE HYPOTENSION FOLLOWING INSERTION OF FEMORAL PROSTHESIS DURING TOTAL HIP REPLACEMENT

AUTHORS: N.E. Sharrock, M.B., Ch. B., K.V. Sanborn, M.D., B. Urquart, R.N., R. Mineo, C.R.N.A., R. Kahn, M.D.
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Introduction

Profound hypotension following insertion of the femoral prosthesis during total hip replacement (THR) has been reported and attributed to methylmethacrylate cement and air or bone marrow fat embolus. [1,2] Patient age, the use of cemented femoral prosthesis, revision surgery and the use of controlled hypotension are factors whose influence on the incidence and severity of this phenomenon have not yet been determined in human subjects.

Methods

Institutional Review Board Approval was obtained to prospectively study these circulatory effects in 807 patients, aged 14 to 93, during THR. Patients were managed under epidural anesthesia with controlled hypotension (>40% reduction in mean arterial pressure (MAP) from baseline). Intraoperative monitoring included 20 ga. radial artery catheter, ECG, pulse oximetry, and nasal O_2. Printed trend recordings of Systolic and mean arterial blood pressure, heart rate (HR) and SaO_2 were saved and analyzed for each patient. Methylmethacrylate cement was used to fix the femoral component in 640 THR's (79.3 %) and 167 were non-cemented THR's (20.7%). Of the cemented THR's, 548 (85.6%) were primary operations and 92 (14.4%) were revisions. Clinically significant hypotension was defined as ↓Sys. BP≥20 mm Hg immediately following insertion of femoral prosthesis. Results were analyzed using Chi-Square contingency tables and ANOVA for group comparisons and unpaired, two-group t-test.

Results

Clinically significant hypotension occurred in 31 of 640 cemented THR's (4.8%), whereas there was no occurrence of clinically significant hypotension among 167 non-cemented THR's p<0.01 (Figure 1). The mean age of patients undergoing cemented THR was significantly greater than that of patients undergoing non-cemented THR; however, within the cemented group of THR's, patient age did not influence the incidence of clinically significant hypotension.

Clinically significant hypotension occurred in 19 of 548 primary cemented THR's (3.5%), and in 12 of 92 revision cemented THR's (13.0%) p<0.0001 (Figure 2).

The effect of hypotensive anesthesia was assessed by dividing 640 cemented THR's into two groups based on MAP immediately prior to insertion of femoral prosthesis. When the MAP just prior to cement fixation of the femoral prosthesis was ≤ 55 mm Hg, there was a lower incidence of clinically significant hypotension p< 0.05 (Figure 3).

Discussion

We conclude that clinically significant hypotension associated with fixation of the femoral prosthesis is 1) directly related to the use of cement; 2) more frequent in revision THR's, 3) independent of age, and 4) less frequent when controlled hypotension is maintained at MAP ≤ 55 mm Hg at the time of insertion of femoral prosthesis.

References

1. Anesthesiology 65:213-216, 1986
2. J Bone and Joint Surg 69-A (6):822-832, 1987

Figure 1.

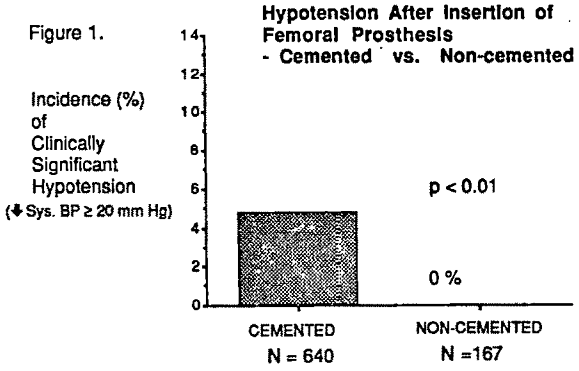


Figure 2.

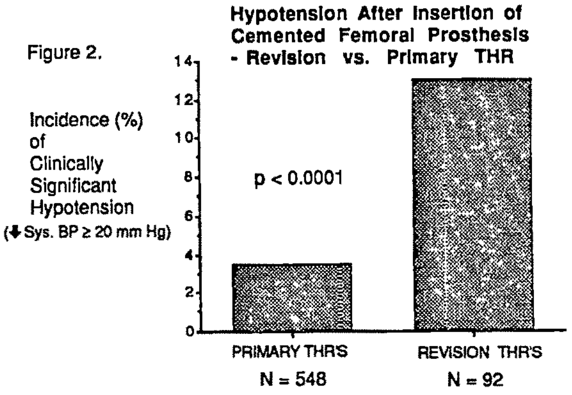
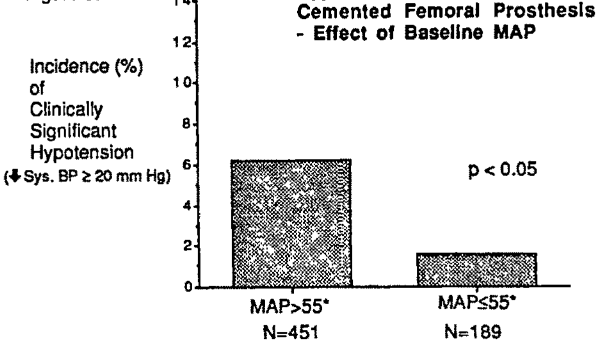


Figure 3.



* Mean Arterial Pressure immediately prior to insertion of femoral prosthesis.

Title: INACCURACY OF ARTERIAL PRESSURE AND HEART RATE IN THE ANESTHESIA RECORD: A STUDY OF HUMAN FACTORS

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Valhalla, New York 10595

Conventionally, arterial pressure (AP) and heart rate (HR) are measured manually every five minutes and recorded in anesthesia charts. Recently, anesthesiologists have used continuous monitoring and display of AP and HR in patients undergoing major surgery along with manual entry of these numbers in conventional anesthesia charts. When uninterrrupted monitoring is required, the machine is probably more reliable than the person in recording.[1] Therefore, we examined the accuracy of AP and HR recorded manually in the anesthesia charts of patients undergoing major surgery and considered human factors associated with inaccuracy.

Methods: With the approval of the Human Investigation Committee, fifty-five patients undergoing surgery for abdominal aortic aneurysm were monitored with ECG and arterial cannulation. Systolic arterial pressure (SAP), diastolic arterial pressure, and the HR were continuously displayed on the monitoring screen. AP and ECG were continuously recorded by a hot pen recorder and on FM tapes throughout anesthesia and surgery. Since continuous recording of AP and ECG were being performed for other research purposes, resident anesthesiologists were unaware that AP and HR recorded in anesthesia charts would be retrospectively compared to continuously recorded data. Comparisons between the SAP and HR recorded in the anesthesia charts (SAP-A, HR-A) and continuously recorded HR (HR-C) and SAP (SAP-C) were made at 3 spots during the peri-induction period and also during surgery at 5 random spots. In addition, whenever SAP-C exceeded 160 mmHg or fell below 90 mmHg, corresponding HR-A and SAP-A were examined. Resident anesthesiologists recording AP and HR were all in their CA-2 or CA-3 years of clinical training. In addition, residents were surveyed to determine normal charting practice.

Results:

1) The relationship between SAP-A and SAP-C and that between HR-A and HR-C in 429 data points are shown in Fig. 1.

2) When SAP-C and HR-C were within the normal range ($100<\text{SAP-C}<140$ mmHg and $60<\text{HR-C}<100$ beats/min.), there were no significant differences between the data of anesthesia charts and that of continuous recording; however, when SAP-C was outside of the normal range, there were significant ($P<0.01$) differences between the data of anesthesia charts and that of continuous recording (Table 1).

3) Seventy-six episodes of hypotension ($\text{SAP-C}<90$ mmHg) were related to duration of episodes and timing of occurance (Table 2).

4) Among the records of 13 resident anesthesiologists, the mean values of ΔSAP ($\Delta\text{SAP}=\text{SAP-A} - \text{SAP-C}$) were not significantly different from each other; however, ΔHR ($\Delta\text{HR}=\text{HR-A} - \text{HR-C}$) was significantly greater in 2 out of 13 residents' records.

5) The majority of residents (16/21) stated that during the induction period SAP and HR were entered in the charts by memory 10-25 minutes later as compared to 5-10 minutes later during surgery. Automated blood pressure records were thought helpful for anesthesiologists in malpractice cases by 12/21 but considered harmful by 9/21 residents.

Discussion: When hypotensive and hypertensive episodes occurred, anesthesia records of SAP tended to be inaccurate. This trend was universal among the records of all residents. Inaccuracy of HR was less and limited to the records of a few residents. Human factors affecting inaccuracy of SAP appear to be multifactorial. Though residents were less busy during surgery as compared to the induction period, inaccuracies continued. The duration of the hypotensive and hypertensive episodes (less than or greater than 5 minutes) does not seem to affect the accuracy of manual recording. A psychological bias and reluctance against recording hypotensive or hypertensive episodes definitely exists.

Figure 1.

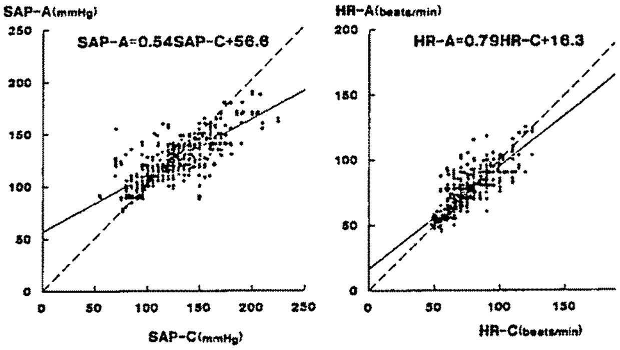

Table 1. Mean values and standard deviations

	Lower range	Normal range	Higher range
SAP-A(mmHg)	104±15	121±11	142±18
SAP-C(mmHg)	88±9	120±10	158±18
ΔSAP(mmHg)	17±17	1±10	-15±15
HR-A(beats/min)	64±10	80±10	99±12
HR-C(beats/min)	60±5	79±8	108±8
ΔHR(beats/min)	2±8	0.4±8	-9±10

Table 2. Mean values and standard deviations

Hypotensive episode	Peri-induction	During surgery
less than 5 minutes	n=15	n=30
SAP-C(mmHg)	78±9	77±5
ΔSAP(mmHg)	31±21	30±19
more than 5 minutes	n=9	n=22
SAP-C(mmHg)	79±8	75±8
ΔSAP(mmHg)	25±9	27±22

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Title: FACTORS INFLUENCING STROKE OUTCOME FOLLOWING CAROTID ENDARTERECTOMY

Authors: F.E. Sieber, M.D., T.J. Toung, M.D., M.N. Diringer, M.D., and H. Wang, M.D.

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Introduction: The decision to recommend carotid endarterectomy is usually based on the presumption that it will reduce the risk of future stroke more than medical therapy. However, this type of analysis fails to take into account the risk of perioperative stroke which has a reported incidence of 2 to 20%. Moreover, when evaluating the risk of perioperative stroke, it is important to consider not just the occurrence of the event, but its severity. To facilitate evaluation of the utility of carotid endarterectomy, it is important to delineate factors associated with perioperative stroke outcome. In previous reports, the small number of perioperative strokes precluded analysis of this question. This study was designed to identify factors associated with outcome from perioperative stroke during carotid endarterectomy.

Methods: This study was approved by the institutional human investigation committee. All available charts of patients who had undergone carotid endarterectomy at this institution between 1979 and 1989 were reviewed and patients sustaining a perioperative stroke were identified. Stroke patients were analyzed for time of stroke occurence, preoperative, intraoperative, and postoperative factors which may contribute to stroke. Based on the Mayo clinic classification[1], preoperative medical, neurologic and angiographic risk factors were recorded for each patient. The intraoperative risk factors included use of a shunt, ischemic cross clamp time and the use of a patch graft. Postoperative blood glucose levels during and following the stroke were determined. In addition, significant events which occurred in relation to the stroke were noted including: perioperative myocardial infarction, surgical complications, blood pressure fluctuations, and hypoxia. Based on the most recent neurologic exam, perioperative strokes were graded as good or poor using the method of Pulsinelli et al.[2] Briefly, good outcome was defined as the ability to return to work or carry on independent activities of daily living. Poor outcome denoted an inability to work, live independently, or death. The good and poor outcome groups were compared using chi-square and student's T-test.

Results: The charts of 561 patients were reviewed. There were 38 perioperative strokes identified giving an incidence of 6.7%. Of these, 23 (60%) occurred postoperatively, with 17 strokes occurring within the first 12 postoperative hours. Fifteen strokes (40%) occurred intraoperatively. Of the 38 strokes, 18 (47%) were classified as good outcome and 20 (53%) as poor outcome. Medical, neurologic and angiographic risk factors were comparable in both groups. Intraoperative ischemic time as well as the use of a shunt was similar among groups. In the poor outcome group 17 patients (85%) had associated events. Surgical complications were the primary factor in 11 patients and contributed to poor outcome in another 2 patients. In contrast, only 3 patients with good outcomes (17%) had surgically related events (chi-square - 7.025; $p<0.0073$). The primary surgical event was carotid occlusion which occurred in 9 poor outcome patients. 2 good outcome patients with suspected carotid occlusion were immediately taken back to the operating room and intraarterial clot removed. Seven (47%) of the intraoperative and 10 (43%) of the postoperative strokes were associated with a significant event. Blood glucose was higher at the time of stroke and during the subsequent week in the poor outcome group.

Discussion: This study demonstrates that the majority of strokes occurring with carotid endarterectomy have their onset within the first 24 postoperative hours. However, neither the time at which the stroke occurs, preoperative stroke risk factors, or intraoperative stroke risk factors influence stroke severity. The major determinant of poor stroke outcome following carotid endarterectomy is the occurrence of a surgical complication, particularly carotid thrombosis. Postoperative hyperglycemia may also play a role, but it is probably a minor one. This study suggests that the anesthesiologist has little ability to further effect the outcome of a major stroke during carotid endarterectomy except to employ currently recommended intraoperative anesthetic management[3]. However, postoperative intensive care assumes an important role in monitoring for carotid occlusion. Early recognition and rapid intervention when these surgical complications occur maximizes the patient's chances for a good outcome following a neurologic event[4].

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Title: USE OF CONTINUOUS VS INTERMITTENT NARCOTIC AFTER CABG SURGERY: EFFECTS ON MYOCARDIAL ISCHEMIA

Authors: D. Siliciano, M.D., M. Hollenberg, M.D., P.Goehner, M.D. and D. Mangano, PhD., M.D.
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Introduction: Currently, sedation is maintained in CABG patients postoperatively with intermittent bolus administration of morphine and a benzodiazepine until the following morning. The early postoperative period is stressful with high levels of plasma catecholamines (1), transient decreases in left ventricular function (2), and frequent (40-60%) myocardial ischemia (3). In noncardiac surgical patients, myocardial ischemia appears to be suppressed by anesthesia (4). To assess whether postoperative anesthesia has an effect on myocardial ischemia following CABG surgery, we compared a continous high dose sufentanil infusion to intermittent doses of morphine.

Methods: After approval of our institutional human investigation committee and after written informed consent was obtained, 63 men for elective CABG were studied. Patients with uninterpretable ECGs (LBBB, WPW) were excluded. Anesthesia was sufentanil 5-10 mcg/kg for induction followed by an infusion of 4.2-6.0 mcg/kg/hr, and up to 0.5 mg/kg of valium. Following bypass patients were randomized to receive either sufentanil 1 mcg/kg as a bolus followed by an infusion of 1 mcg/kg/hr (Group S, N=32) or morphine up to 2 mg/kg (Group M, N=31). In the ICU Group S continued to receive the infusion of 1 mcg/kg/hr while Group M received intermittent doses of morphine (1-10 mg iv every 30 minutes prn). Both groups received midazolam 1-4 mg iv every 20 minutes prn. Sedation was discontinued at 04:00. No other aspects of clinical care were dictated by protocol. Patients were monitored continuously with 2 channel (CM5, CC5) Holter monitors. Ischemic episodes (IEs) were defined as a ≥1mm ST depression at J+60 or a ≥2mm elevation at J, which was transient and lasted for ≥60 seconds. Hemodynamics were recorded every minute by a computer interfaced with the bedside monitor. Statistical analyses were performed using unpaired t tests. Results are shown as mean ± standard deviation.

Results: Preoperatively, patients in Groups S and M were similar in weight, age, EF<40%, left main disease, unstable angina, hypertension and beta blocker use. However fewer diabetics were in Group S than Group M (13 vs 37%; p=0.02). The two groups received similar amounts of sufentanil and valium in the OR, and fluids in the ICU. Time to extubation was also similar for both groups. After bypass, Group S received a total of 15.9 (±3.1) mcg/kg sufentanil, compared with 1.6 (± 0.6) mg/kg of morphine for Group M. Group S received less midazolam than Group M (0.11 vs 0.23 mg/kg; p<0.005). In Group S (vs Group M) there was a trend toward lower mean heart rates (86 vs 92) and lower systolic pressures (116 vs 124), and a significantly lower double product (10,006 vs 11,515, p<0.05).

In the OR, the incidence (41 vs 42%) and severity of IEs postbypass was similar in the two groups, as was the incidence (28 vs 29%) of new IEs in the ICU. However, in Group S, the IEs that occurred in the ICU tended to be shorter, and had significantly smaller ST deviation and area under the curve (AUC) than in Group M (see Table 1).

Discussion: These data demonstrate that continuous administration of high doses of sufentanil, versus prn administration of morphine, can blunt the severity of IEs that occur in the ICU following CABG surgery.

TABLE 1: Severity of Ischemic Episodes in the ICU

	Group S	Group M	p=
Incidence of Ischemia	28%	29%	
mean Duration (min)	71 ± 76	153 ± 122	0.07
mean ST Change (mm)	1.5 ± 0.5	2.1 ± 0.7	0.04
mean AUC (mm^2)	64 ± 87	405 ± 535	0.05

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Title: EFFECT OF BUSPIRONE, A 5HT1A AGONIST ON ISOFLURANE MAC IN RATS: A MODEL FOR MEMBRANE-RECEPTOR INTERACTION

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Introduction: Buspirone (Buspar^{R}) is a 5HT1A partial agonist with anxiolytic properties which does not produce sedation or muscle relaxation.[1] As patients may present for surgery during chronic buspirone therapy, it is of interest to know the potential interactions with general anesthetics. In addition, as the 5HT1A receptor is a well characterized membrane bound structure with intimate connection to a variety of effector mechanisms including G-protein, ionic channels, and adenylate cyclase, the interaction of buspirone with volatile anesthetics provides an interesting model of drug interaction which may further elucidate the mechanism of volatile anesthetics.

Methods: This study was approved by the Animal Care and Use Committee of our institution. Sprague-Dawley rats (350-500 g) were placed in groups of four in an air-tight, heat controlled chamber which was filled with Isoflurance-O_2. O_2, CO_2, and isoflurane concentrations were measured continuously with a Rascal Raman spectrometer (Albion Instruments Salt Lake City, Utah). Rectal temperatures were monitored with a Yellow Springs telethermometer and maintained at 37.5 + 1.5 degrees C. Initial concentrations were maintained for a minimum of 30 minutes. A standard stimulus of a clamp applied to the distal third of the tail for 60 seconds was utilized to test for purposely movement of the head or feet.[2] This procedure was repeated until purposeful movement was detected in all four animals. The ED_{50} (equivalent to MAC-minimum alveolar concentration) was defined as the mean of the concentration at which movement occurred and that at which movement did not occur. The concentration was then increased and buspirone was injected intraperitoneally. Three groups of four rats were injected for each dose of 1 mg/kg, 10 mg/kg, or 100 mg/kg. The procedure was then repeated. The results were analyzed by a paired T-Test comparison of the mean difference between ED_{50} before and after injection of buspirone.

Results: Table 1 displays the results of the controls and experimental groups for each of the three dose regimens. The P values refer to the mean differences reported. A biphasic response is evident in Figure 1. At 1 and 10 mg/kg, doses approximating human dosage, isoflurane requirements increase significantly. However, at 100 mg/kg there is a significant decrease in isoflurane MAC.

Discussion: In contrast to the well documented interaction between benzodiazepines and volatile anesthetics,[3] buspirone elicits an opposite response. This may be associated with the known lack of sedative effect of this novel anxiolytic medication. The mechanism of this unexpected attenuation of isoflurane effect by busiprone remains to be elucidated. The correlation of this interaction to human patients has not been explored.

Work is presently underway to further evaluate this preliminary data which should provide a macroscopic perspective from which to probe the underlying molecular mechanism of the effect of volatile anesthetics on membrane bound receptor-effector complexes.

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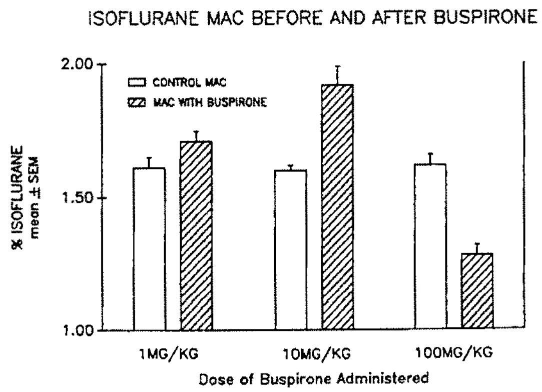
TABLE 1

Isoflurane MAC with and without Buspirone

Dose mg/kg	Inspired ED50 (%) Control	with Drug	Diff	P
1	1.61±0.04	1.73±0.04	+0.12	0.0024
10	1.60±0.02	1.92±0.07	+0.32	0.0003
100	1.62±0.04	1.28±0.04	-0.34	0.0001

FIGURE 1


ISOFLURANE MAC BEFORE AND AFTER BUSPIRONE

TITLE: **COMPARISON OF BUPIVACAINE, BUPIVACAINE/LIDOCAINE, AND BUPIVACAINE/FENTANYL FOR LABOR ANALGESIA**

AUTHORS: R. S. Sinatra, M.D., Ph.D.; R. Goldstein, M.D.; F. B. Sevarino, M.D.
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INTRODUCTION: Motor blockade, shivering and hypotension are undesirable effects of epidural analgesia, while the need for frequent reinforcements is a drawback to the intermittent dosing technique. We compared three therapies commonly used at our institution to delineate superiority at minimizing the aforementioned side effects while still utilizing the intermittent dosing technique.

METHODS: Following IRB approval and informed written consent, 37 healthy, term parturients were randomly assigned to 1 of 3 treatment groups. Group Bupivacaine (n=13) received 5 cc of 0.5% bupivacaine + epinephrine 1:200,000 followed by 1-5 cc additional of 0.5% bupivacaine based on height. Group Bupivacaine/Lidocaine (n=13) received a 5 cc mixture of 0.25% bupivacaine + 1% lidocaine + epinephrine 1:400,000 followed by an additional 1-5 cc based on height. Group Bupivacaine/Fentanyl (n=11) received 5 cc of 0.5% bupivacaine + epinephrine 1:200,000 followed by 50 ug of fentanyl in 10 cc 0.9% NaCL (total volume 15 cc). All medication was administered in divided doses through an L_{3-4} catheter with patients in LUD. All patients received a minimum of 1,200 cc of Ringers Lactate, IV, prior to epidural placement. A blinded observer collected data before the block and every 5 min for the first 30 min after the total dose was administered and then every 30 min until a reinforcement was requested. Efficacy of epidural analgesia was assessed with visual analogue scales (VAS) for pain and satisfaction. The presence and severity of shivering and pruritus, blood pressure, heart rate, ephedrine dosage, sensory level, motor blockade and changes in fetal heart rate were also noted. Data analysis utilized ANOVA, KRUSKAL-WALLIS, and chi-square tests with p<0.05 as statistically significant.

RESULTS: There were no significant differences between treatment groups in demographics, fluid bolus, starting or low BP, ephedrine usage, pruritus and sensory level. There were no significant differences with regard to baseline pain score, lowest pain score achieved, time to lowest pain score, highest satisfaction score achieved, and time to highest satisfaction score.

	Time Lowest Pain (VAS) (Min.)	Time Highest Satisfaction (Min.)
B	14.6±8.2	15.3±9.2
B+L	14.2±10.5	13.4±11.0
B+F	13.6±5.9	14.0±5.8

Patients receiving bupivacaine/fentanyl had the lowest degree of motor blockade, the lowest incidence and severity of shivering, and the longest duration of analgesia (p<0.050.

	Motor Blockade	Shivering Scale	Duration (Min.)
B	1.53±0.96	0.85±0.55	116.9±19.6
B+L	1.53±1.12	0.77±0.73	126.3±32.9
B+F	0.18±0.40*	0.18±0.40*	165.1±25.4*

Shivering 0 = none; 1 = mild; 2 = moderate; 3 = severe
Motor 0 = prolonged leg lift; 1 = brief leg lift; 2 = bend knees; 3 = wiggle toes; 4 = no movement. * p < 0.05

DISCUSSION: While all agents provided effective and reliable analgesia with high patient satisfaction, patients in Group bupivacaine/fentanyl achieved the longest duration of analgesia with the lowest degree of shivering and motor blockade. These properties are desirable to the anesthesiologist and obstetrician (i.e., longer duration of analgesia, effective pushing during stage II), nurse (patient ability to move), and patient (less frequent shivering). Therefore, we find bupivacaine/fentanyl to be superior to bupivacaine and bupivacaine for labor analgesia.

TITLE: COMPARISON OF CARDIOPULMONARY AND ANESTHETIC RESPONSE TO VITAL CAPACITY RAPID INHALATION INDUCTION (VCRII) WITH HALOTHANE (H), ISOFLURANE (I), AND ENFLURANE (E)

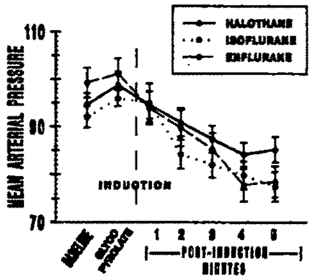
AUTHORS: S. A. Siriwardhana FFARCS, A. Kawas M.D., R. G. Unsell M.D., S. L M. L. Cosentino D.D.S., E. R. Johnson M.D., and A. H. Giesecke M.D.
AFFILIATION: Department of Anesthesiology, University of Texas Southwestern Medical School, Dallas, Texas 75235, U.S.A.

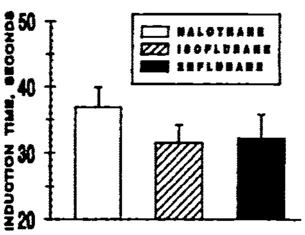
INTRODUCTION: The inhalational induction of anesthesia is usually unpopular with both patients and anesthesiologists. The prolonged induction time, prolonged excitement phase, difficulty in maintaining the airway, laryngospasm, and vomiting are the main drawbacks. To provide a better method of inhalation induction of anaesthesia in cooperative adults it has been suggested that a single breath vital capacity using higher inspired concentrations of halothane and oxygen decreases the induction time, which is effective, safe, and well accepted by the patients. The addition of N_2O to the inhaled mixture will decrease the concentration of vapor required to induce anesthesia.

Relative cardiovascular stability was a notable finding in these techniques and the induction time was unaffected by the age, weight, and smoking habits. The technique was found to be acceptable to most patients studied and was proposed as a safe alternative to IV induction in cooperative adults. Uptake and distriibution of anesthetic gases and vapors depends on inhaled concentration, alveolar ventilation, solubility, pulmonary blood flow, alveolar to venous anesthetic gradient, alveolar membranes, the ventilation perfusion relationships, second gas effect, cardiac output, secondary saturation of body tissues, metabolism and the anesthesia circuitry. Taking most of these factors into careful consideration we used this technique to compare the cardiopulmonary and anesthetic effects to halothane, enflurane, and isoflurane.

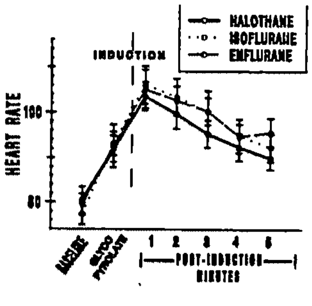
METHODS: With IRB approval and written consent of patients we studied 62 ASA I unpremedicated patients who underwent lararascopic tubal ligation under general anesthesia. All received glycopyrrolate 0.3 mg IV five minutes prior to induction. The anesthetic circuit was filled with N_2O/O_2 vapors and using a clear mask all patients had vital capacity inhalation inductions with equipotent inspired concentrations (8 MAC in 66% N_2O) of either halothane (2.4-3%, 21 patients), isoflurane (3.8-4%, 20 patients), or enflurane (4.8-5%, 20 patients). High flows were used. Patients were randomly allocated to groups and vapors and gases were analyzed breath to breath by using Puritan-Bennett 253 gas analyzer.

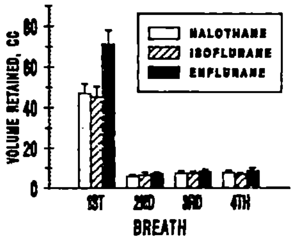
RESULTS: Parameters listed were studied and compared: (1) The three groups were not significantly different with respect to age, weight, duration of anesthesia and surgery, and vital capacity (MANOVA P=5). (2) Mean induction time in seconds (time taken to disappearance of eyelash reflex) were H-36.2±1.5, I-31.5±2.5, E-32.2± 3.1. Induction times were not statistically significant between the groups. (3) At each time mean arterial pressure and HR were not significantly different between groups (although MAP dropped across time). Saturation remained the same and no incidence of any arrhythmias was noted. (4) Movements during induction were not statistically significant. Coughing was significant in I and E groups (H=O, I+28%, E=20%). There were no seizures or vomiting. (5) Amount of vapor volume retained is very high with the first breath and diminished after induction as the respiratory depression occurred taking vital capacity breath. (6) Mean end tidal CO_2 concentration for first four breaths after induction were not significantly different between the groups (H=31,33,34,32, I=31,32,32,31, E=31,33,34,33).





We conclude that VCRII with 8 MAC of either H, I, or E in N_2O and O_2 is a safe technique in cooperative unpremedicated adults. There appears to be enough vapor uptake during vital capacity breath to cause amnesia and loss of eyelash reflex. All vapors in equipotent doses behave similarly except coughing with I and E. In spite of its pungent smell, I offers a safe alternative to others because of its low metabolism, less hepatotoxicity, and lack of seizure activity.





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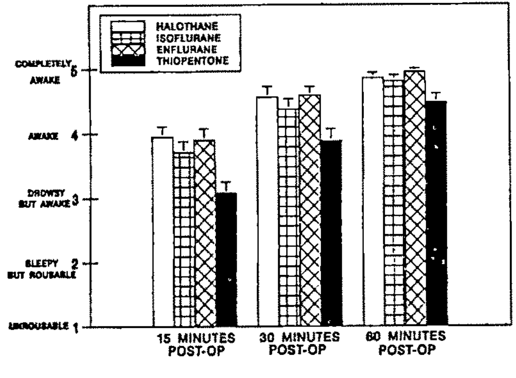
TITLE: *RECOVERY FROM RAPID INHALATION INDUCTIONS AND THIOPENTAL FOR OUTPATIENT ANESTHESIA*
AUTHORS: *S. A. Siriwardhana FFARCS, A. Kawas M.D., R. G. Unsell M.D., S. L M. L. Cosentino D.D.S., E. R. Johnson M.D., and A. H. Giesecke M.D.*
AFFILIATION: *Department of Anesthesiology, University of Texas Southwestern Medical School, Dallas, Texas, U.S.A.*

INTRODUCTION: *The inhalational induction of anesthesia is usually unpopular with both patients and anesthesiologists. To provide a better method of inhalation induction of anaesthesia in cooperative adults it has been suggested that a single breath vital capacity using higher concentration of vapors and oxygen decreases the induction time, which is effective, safe, and well accepted by the patients. Inhalation inductions with newer, less soluble vapors claim prompt and full recovery which might be of use in out-patient anesthesia. We compare this effect using vital capacity breath of equipotent (8 MAC in 66% on N$_2$O) halothane (H) 24-3%, isoflurane (I) 3.8-4%, and enflurane (E) 4.0-5% with IV thiopental (4 mg/kg).*

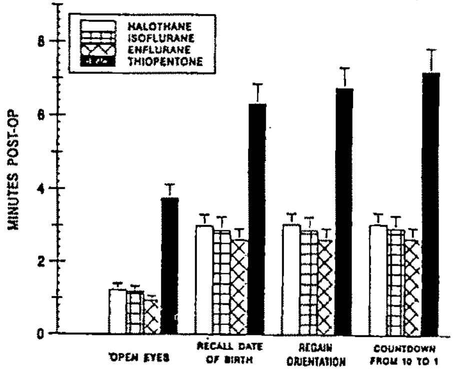
METHODS: *With IRB approval and obtained written consent, 87 unpremedicated ASA I females for lararascopic tubal ligation were included in the study and were randomly divided into four groups receiving H, I, E, and STP for induction.*

Glycopyrrolate 0.3 mg was given five minutes prior to induction. After induction (loss of eyelash reflex) inspired concentrations were reduced and discontinued after five minutes. Anesthesia was maintained with N$_2$O/O$_2$ 6L/3L, sufentanil 0.5 mcg·kg^{-1} and vecuronium 1 mg·kg^{-1}. Reversal was with glycopyrrolate and neostigmine.

CLINICAL ASSESSMENT OF RECOVERY



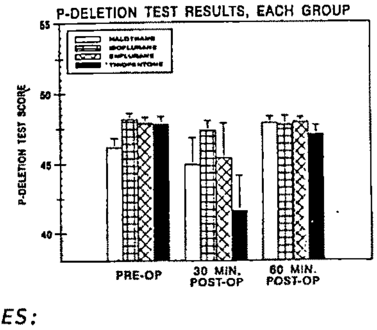
INITIAL RECOVERY ASSESSMENTS



RESULTS: *Groups were not significantly different with respect to age, weight, duration of anesthesia and operation, induction time, and vital capacity (MANOVA P=0.15). (2) Initial recovery times (eye opening, countdown from 10 to 1, orientation, give DOB) were significantly shorter in the vapor groups compared to STP but among the vapor groups they were not significantly different (ANOVA, Bonferroni post hoc test). (3) Postop nausea and vomiting did not differ significantly (Chi-square=0.8 P=0.8). (4) The patient's questionnaire for vapor groups revealed the following. All remembered holding the breath and the smell. The majority said it's not unpleasant (H=95.2%, I=95.2%, E=90%). Number of breaths remembered (1st breath H=57%, I=85%, E=85% 2nd breath H=42%, I=15%, E=15%). Willing to have this form of anesthetic again were H=90%, I=95%, E=85%. (5) Clinical recovery scores given by an independent observer at 3 different times showed a lower score in the STP group (P=.0003 Rpt measures ANOVA). (6) Psychomotor functions tested ("p" deletion test) at 3 times showed no significant difference between 4 groups.*

DISCUSSION: *We believe the initial recovery is more prompt and complete with the vapor groups than STP group and they can be useful in outpatient anesthesia as alternatives. Patients who received isoflurane and enflurane recover slightly better than those receiving more soluble halothane, although it is statistically not very significant.*

P-DELETION TEST RESULTS, EACH GROUP



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5. *Eger EI, II: Uptake and distribution of inhaled anaesthetics. In Miller RD, ed: Anesthesia. 2nd edition. Churchill-Livingstone, 1986, pp. 625-648.*

TITLE: INCIDENCE OF HEADACHE FOLLOWING SUBARACHNOID BLOCKADE WITH 29g SPINAL NEEDLE FOR POSTPARTUM (24-48 HRS) TUBAL LIGATION

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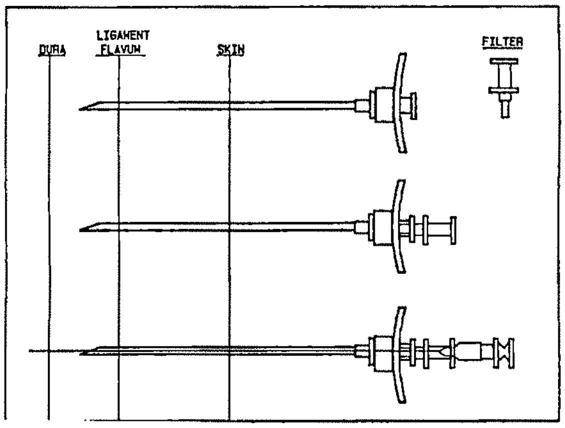
INTRODUCTION: Post dural puncture headache (PDPH) has been a known common complication since the first spinal anesthetic. The needle size is the most readily recognized contributing factor. The larger the bore, the greater the incidence of headache. The angle of approach can also influence fluid transudation. Age is also important. The younger (presumably healthier) patients paradoxically have a higher probability of post-spinal headache (12% in women versus 9% in men in Vandam study) (1). Ambulation after dural puncture is a controversial subject. Jones reported that the incidence of headache was not different between groups kept at bed rest for varying periods of time postoperatively. The state of hydration, straining, and, rarely, even air travel also have been associated with onset of symptoms. Postpartum tubal ligation is commonly done under subarachnoid block (SAB). The incidence of PDPH is greater in the parturient (22%) than in non-pregnant (11% in Vandam study). Higher incidence of PDPH has also been reported in 24-48 hours postpartum patients using 22g and 25g needles (24% and 20%). (2) Our study is to determine the incidence of PDPH with 29g spinal needle.

METHOD: With IRB approval and written consent from patients we studied the incidence of PDPH in 100 patients who had tubal ligation done within 24-48 hours after vaginal delivery. All patients were premedicated with Bicitra 20-30 ml p.o. and diazepam 10 mg p.o. They all received at least 1000 ml of Ringers solution 15-30 minutes prior to SAB. Combined spinal epidural technique was used with 17g 3.5" long epidural needle and 29g 5.5" long spinal needle (B&D) in either sitting or right lateral decubitus position. L_{3-4} interspace was used. Single dural puncture was easily made by the combined technique and 5% lidocaine in 7.5% dextrose was used. Patients were interviewed by telephone 3-7 days after discharge from the hospital. None of them were allowed to lie flat for more than 1-2 hours after SAB.

RESULTS: Six patients were excluded from the study (two were given general anesthesia for surgical complications and four had to be reinjected with local anesthetics through 25g spinal needles as the first SAB was not adequate). Sixteen patients were not able to be contacted. Out of the 58 patients contacted, only two had slight headache on 3rd or 4th days, lasting for less than two hours and did not have any treatment. Fifteen complained of backache at the site of the epidural insertion. No dural puncture occurred with the epidural needle and no other complications were reported.



DISCUSSION: Although high incidence of PDPH was reported by other authors in postpartum patients, these data show this can be minimized to a very low incidence by using 29g spinal needles. The technical difficulties to introduce these needles could be overcome by using the combined spinal epidural technique to a great extent.

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USE OF INTRANASAL MIDAZOLAM IN PRESCHOOL CHILDREN

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Introduction

We evaluated the efficacy of intranasal midazolam given 7 1/2 minutes prior to parental separation in alleviating separation anxiety and providing a calmer induction in children 8 months - 2 years undergoing PE tube placement. Midazolam is frequently used as a premedication in adults and older children because of its anxiolytic, amnestic, and sedating properties. Although premedication for younger children could be desirable to decrease separation anxiety and fear, it has not been widely used because of the concern that oversedation might delay discharge.

Methods

Following approval by the institutional Human Subjects Committee, informed parental consent was obtained for 55 ASA I and II patients (8 months - 2 years) undergoing PE tube placement. The patients were randomly assigned into four groups. All groups received an equal volume of nasal drops, 0.12 cc/kg, which was administered in the presence of the parents. Group I received normal saline; Group 2 received 0.2 mg/kg midazolam with normal saline; Group 3 received 0.4 mg/kg midazolam with normal saline, and Group 4 received 0.6 mg/kg midazolam. Only the pharmacist knew the patient group identity.

The level of sedation was scored as follows:[5] (1) agitated, (2) alert, (3) calm, (4) drowsy and (5) asleep. Each patient was scored for 10 minutes at 2 1/2 minute intervals following administration of the nasal drops. The patient was separated from his parents at 7 1/2 minutes following administration of the nasal drops and his response noted. An inhalational induction with halothane was initiated (after monitors were placed) 10 minutes after the nasal drops, and the child's response noted. Postoperatively the child was returned to the PACU where the level of sedation was scored at 2 1/2 minute intervals for 20 minutes. The time of discharge home was also noted. Data was analyzed by ANOVA, chi squared, Bonferri correction, and Kruskal-Wallis, with Mann-Whitney for intragroup comparisons on the nonparametric data.

Results

Mean age and weight were similar among the four groups. Except for the control group, most children were adequately sedated by 7 1/2 minutes. The differences in parental separation scores was statistically significant for Groups 3 and 4 ($p < 0.001$) (Fig. 1). The difference between Group 1 and Group 2 was not statistically significant. The difference in induction scores between the control group and those receiving midazolam was statistically significant ($P < 0.002$). (Fig. 1). There was no statistical difference in operating room time among the four groups, although Group 1 patients required a significant higher dose of halothane ($p<0.05$). The time to full return of consciousness was not statistically different among the four groups. There was no statistical difference in discharge times for any of the four groups. No change in O_2 saturation was noted during preop monitoring on room air, intraoperatively, or postoperatively. No significant side effects were noted in any child.

Discussion

This study demonstrated that intranasal midazolam is an effective premedication which can be used in young children undergoing short procedures. Although the control group patients became calmer as they became accustomed to the observer, this effect did not last through induction. Seven and a half minutes allowed most children in the group receiving midazolam to separate easily from their parents. Many of these children became mildly euphoric when their sedation score reached 3. As the children relaxed and became calm, most parents appeared more comfortable. Children receiving 0.4 and 0.6 mg/kg of midazolam had much smoother inductions requiring lower doses of halothane during induction. Children receiving midazolam woke up calmer and were more cooperative than children in the control group. Use of midazolam did not delay discharge from the PACU. Intranasal midazolam in doses of 0.4 mg/kg and 0.6 mg/kg should be considered as a premedication in young children.

FIGURE 1

Intranasal Midazolam Response

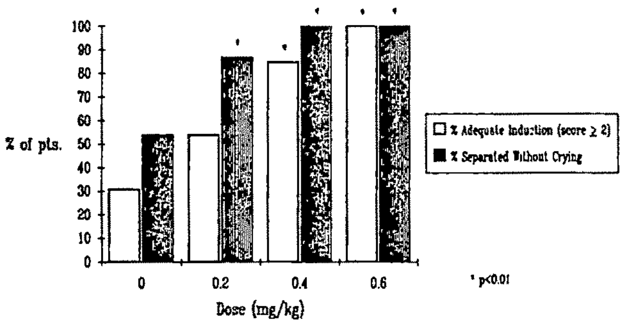

Table I
Intranasal Midazolam Data

Group Number	1	2	3	4	p
Number of pts	13	13	15	14	
Maximum halothane dose (induction)	4.31±0.26	3.42±0.36	2.81±0.11	2.75±0.14	<0.05*
Wake-up time	6.31±3.12	12.38±2.96	12.25±4.19	10.21±3.10	0.553
Discharge time home	40.92±3.05	34.83±1.46	41.15±3.52	38.79±3.2	0.438

Values are mean±SEM * for groups 3 and 4 only

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Title: EMERGENCE FROM DESFLURANE ANESTHESIA IS MORE RAPID THAN FROM ISOFLURANE

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Introduction: Desflurane (difluoromethyl 1,1,1,2 tetrafluoroethyl ether, previously referred to as I-653) is a new volatile anesthetic agent currently under evaluation for possible release for clinical use in the United States. The blood:gas solubility coefficient of desflurane (0.42) is similar to that for nitrous oxide (0.44) and significantly lower than that for isoflurane (1.4), suggesting that desflurane should allow rapid induction of and emergence from anesthesia.[1] As part of a protocol designed to compare desflurane to isoflurane, we have measured the time from discontinuation of the anesthetic until return of consciousness with the two anesthetics, and have demonstrated that desflurane does indeed result in a faster "wake-up."

Methods: Ten patients (ASA Class 1 or 2) scheduled for surgery were studied. Intraabdominal, intrathoracic, and intracranial operations were excluded (because the protocol was designed to study the use of muscle relaxants and therefore restricted their use). Written, informed consent was obtained, and the study was approved by the Institutional Review Board. Subjects were assigned to the isoflurane or desflurane groups (5 each) by reference to a random number table. Premedication was 0.03 mg/kg midazolam given IV after the intravenous line was established in the OR area. Patients were monitored with a blood pressure cuff, electrocardiograph, pulse oximeter, capnograph, axillary temperature probe (esophageal after induction), and a Datex 254 airway gas monitor specially modified for the capability of measuring desflurane concentrations (Puritan Bennett Corp.). Anesthesia was induced with thiopental (5 mg/kg), and the patients were ventilated by mask with slowly increasing concentrations of the assigned anesthetic agent in 60% nitrous oxide/40% oxygen. Most patients received an additional dose of thiopental (1-2 mg/kg) to facilitate continued ventilation with increasing concentrations of desflurane or isoflurane. When the patient was deemed ready for intubation by the attending anesthesiologist, laryngoscopy was performed, the trachea sprayed with lidocaine (160 mg), and intubated without the use of muscle relaxants. The anesthetic agent was then adjusted to give a stable end-tidal concentration of 0.65 MAC (4.7% for desflurane, 0.8 % for isoflurane, using MAC values of 7.25 % and 1.28 %, respectively) which was maintained throughout the surgery. End-tidal CO_2 was maintained between 30-35 torr. At the end of the operation, the studied agent and nitrous oxide were simultaneously discontinued, and the patient was ventilated with 100% oxygen at a total fresh gas flow of 5 liters/min, keeping the end-tidal CO_2 at 30-35 torr. When spontaneous ventilation resumed, the patient was allowed to breath without assistance. Once each minute after the anesthetics were discontinued, the patient was asked to open his/her eyes, and to squeeze the investigator's hand. The time of the first positive response to each command was recorded, and the average of the two is reported as the "wake-up" time. Typically, these differed by 0-2 minutes. Since emergence time is dependent on total anesthesia time, subjects in the two groups were paired by anesthesia time (time from induction until discontinuation of the anesthetic), with the longest desflurane exposure paired with longest isoflurane exposure, second longest desflurane with second longest isoflurane exposure, etc. The "wake-up" times were compared with a paired t-test. Data are expressed as means ± SEM (n=5).

Results: Average ages of the two groups were the same, 47.2 ± 7 for desflurane and 48.4 ± 8 for isoflurane. Average exposure was significantly longer ($p < 0.05$) in the desflurane group, 115 ± 11 minutes, versus 88± 19 minutes for the isoflurane. The data is illustrated in the table below, and demonstrates that despite this longer exposure to desflurane, the time from discontinuation of the anesthetic until "wake-up" was shorter for desflurane, 10.6 ± 1.1 minutes, versus 13.4 ± 1.0 minutes for the isoflurane group ($p < 0.01$).

	DESFLURANE		ISOFLURANE	
	wake-up time(min)	anesth. time	wake-up time	anesth. time
	10.5	145	13.0	153
	8.5	134	12.0	107
	8.0	115	10.5	69
	13.5	98	16.0	62
	12.5	84	15.5	51
Avg	**10.6**	**115**	**13.4**	**88**

Discussion: Desflurane does appear to lead to a more rapid emergence than isoflurane when given with nitrous oxide at a moderate (0.65 MAC) dose. The modest effect reported here may become more significant when more patients are studied, with more sensitive tests of level of consciousness and "street-worthiness", especially for outpatients, used to assess recovery. With a low blood and tissue solubility, the total amount of desflurane absorbed by patients should be less than isoflurane, and the effect on emergence may be greater with increased exposure (time or concentration). In a small group (7 patients) given 1.25 MAC isoflurane or desflurane with 60 % nitrous oxide, wake-up times were 31 ± 6 minutes for isoflurane and 15 ± 3 minutes for desflurane. These data, however, did not achieve statistical significance due to small sample size. Further work in this area is proceeding. Clinically, desflurane appears similar to isoflurane as regards hemodynamic and muscle relaxant effects. Studies are ongoing in several centers to elucidate the clinical potential of this new anesthetic.

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TITLE: PERIOPERATIVE DOWN-REGULATION OF THE β-ADRENERGIC RECEPTOR/ADENYLATE CYCLASE SYSTEM OF HUMAN LYMPHOCYTES

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Introduction: One of the primary areas of interest and research in anesthesiology is the response of the sympathetic nervous system (SNS) to the stress of the perioperative period. Many studies have documented increases in circulating catecholamines perioperatively. It is well established that chronic or acute increases in catecholamine levels can can a "reflex" down-regulation or desensitization of the receptor system on many cells, with significant physiological and clinical implications Only one study has examined whether increased hormonal levels in the perioperative period might cause a down-regulation of target receptors and/or desensitization of tissue response to agonists, reporting no change in the number or binding properties of α-2 adrenergic receptors on platelelets during cardiopulmonary bypass.[1] Alpha-2 receptors, however, are resistant to down-regulation relative to β-adrenergic receptors.[2] The human lymphocyte has proven to be an excellent, available model for the study of changes in β-receptor properties on other, less-accessible organs.[3] We have initiated an investigation into changes in the β-receptor/adenylate cyclase system of human lymphocytes in patients undergoing surgery involving cardiopulmonary bypass (CPB).

Methods: Nine subjects undergoing heart surgery including CPB were studied. The study was approved by the Institutional Review Board, and informed consent was obtained. Blood (40 ml) was taken from indwelling catheters before anesthetic induction (control) and the morning of the first postoperative day (POD #1). A portion of the blood was used for assay of plasma catecholamines by HPLC. At each time point, lymphocytes were isolated,[4] and basal and maximal (5×10^{-6} M) isoproterenol-stimulated cyclic AMP production was determined from 1×10^6 cells incubated for 12 minutes at 37° in the presence of the phosphodiesterase inhibitor 2-isobutylmethylxanthine. Each subject's pre-induction basal and isoproterenol-stimulated cAMP production served as his/her own control. Data are mean ± SEM (N=9).

Results: Basal (unstimulated) cyclic AMP was decreased in 8 of 9 patients, averaging 9.32 ± 1.9 pmoles/10^6 cells pre-induction, and 5.2 ± 1.2 postoperatively ($p<0.05$). The amount of cyclic AMP produced by isoproterenol stimulation was less postoperatively in all patients studied (Figure 1). Isoproterenol-stimulated cAMP was 31.9 ± 5.9 initially, and 17.4 ± 5.0 postoperatively ($p<0.01$); however, isoproterenol increased cAMP by 3.4-fold at both time points.

Conclusions. This work represents the first demonstration of perioperative changes in the β-adrenergic receptor/adenylate cyclase system. By the first day after CPB, there is evidence of a decrease in the ability of lymphocytes to generate cyclic AMP. Of note, cells taken immediately after bypass from several patients did not show this consistent effect, suggesting that such "desensitization" postoperatively is not simply due to damage inflicted on lymphocytes by the pump. The fact that basal and stimulated cAMP are decreased, but the ability of isoproterenol to increase cAMP is retained may indicate that the molecular alteration in the receptor/cyclase complex is "distal" to the receptor, e.g., the GTP binding-protein which couples receptor occupancy to effector activation, or cyclase itself. The molecular site and mechanism of this metabolic alteration is now under investigation. Interestly, a recent report suggests a comparable deterioration of the β-receptor/adenylate cyclase sytem in human endotoxic shock.[5] Information about changes in target organ responsiveness is essential to rational physiological understanding or pharmacological manipulation of sympathetic nervous system activation and regulation. Future studies will investigate how clinical status and anesthetic and perioperative care might impact upon the physiological or pathophysiological metabolic regulation.

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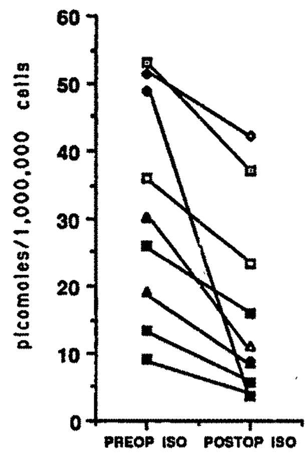
Figure 1. Graph illustrating the actual cAMP data from first 9 patients studied. All 9 demonstate a decrease in isoproterenol (5×10^{-6} M)-stimulated cAMP from lymphocytes on first postoperative day after surgery including cardiopulmonary bypass.

ISOPROTERENOL-STIMULATED CYCLIC AMP



Title: **ALPHA ADRENERGIC AGONIST DRUGS AND EMERGENCE FROM CARDIOPULMONARY BYPASS**

Authors: CE Smith MD, TL Higgins MD, EJ Kraenzler MD, NJ Starr MD, JP Coyle MD, MG Licina MD

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Introduction Schwinn et al (1) reported that the pressor effect of phenylephrine may be impaired in anesthetized patients with low ejection fractions and congestive heart failure undergoing coronary artery surgery prior to cardiopulmonary bypass (CPB). However, this difference was not observed during CPB after application of the aortic cross clamp. The objective of this study was to characterize the relation between preoperative left ventricular dysfunction and requirement for alpha adrenoceptor agonist drugs in patients undergoing coronary artery surgery during emergence from CPB.

Methods Institutional review board approval was obtained. Since participation in this descriptive study did not alter perioperative care, informed consent from each patient was deemed unnecessary.
We studied 102 patients undergoing elective primary or redo coronary artery bypass surgery. Left ventricular function was evaluated subjectively by examination of the 30 degree right anterior oblique left ventriculogram. Group 1 consisted of 75 patients with normal or mild impairment in left ventricular function, whereas group 2 consisted of 27 patients with moderate-severe left ventricular dysfunction. Cardiovascular parameters were measured at a) baseline, b) during hypothermic bypass with the aorta clamped, c) during normothermic bypass after unclamping, and 1 and 15 minutes after separation from bypass. During CPB, non-pulsatile flow (equivalent to cardiac output), systemic hypothermia, electrolyte priming solutions and temperature uncorrected (pH stat) blood gases were employed. Patients were weaned from CPB after rewarming to a bladder temperature of 37° C and correction of serum ionized calcium. Inotropic drug therapy was given for cardiac indices (CI) < 2.0 L/min/m^2 despite optimal heart rate and ventricular filling pressures. Phenylephrine was given alone or with inotropes to maintain mean arterial pressure (MAP) at preoperative levels (generally between 60 and 80 mmHg). Norepeinephrine infusion was used for severe hypotension ($MAP < 50$ mmHg) associated with low systemic vascular resitance ($SVR < 600$ dynes.sec.cm^{-5}). Statistical analysis was with Chi Square and Student's t with the Bonferroni correction where applicable. Results are expressed as mean values ± SEM. A P value < 0.05 was considered significant.

Results Preoperative and intaoperative patient data were similar except that group 2 had a higher incidence of myocardial infarction. Thirty-seven patients in group 1 (49%) and 11 patients in group 2 (39%) required some form of inotropic and/or vasopressor support during weaning from bypass (p = NS). Group 2 required significantly higher doses of phenylephrine after bypass compared with group 1 (1.69 ± 0.70 ug, n = 8 vs 0.24 ± 0.04 ug, n = 27, $p < 0.05$. Similarly, the dose of norepinephrine in group 2 was 3.3 times that in group 1 (10 ± 6 ug/min, n = 2 vs 3 ± 0.6 ug/min, n = 2, p = NS). The dose of calcium chloride was similar between groups 1 (1.0 ± 0.05 g) and 2 (1.1 ± 0.11 g), as was the dose of dobutamine (6.7 ± 0.7 vs 6.3 ± 0.9 ug/kg/min, respectively).

Discussion Following coronary artery revascularization, patients with moderate-severe left ventricular dysfunction may require higher doses of alpha-adrenoceptor agonists compared with patients with normal or mildly impaired left ventricular function. This decreased alpha-adrenergic responsiveness may be due to differences in alpha adrenoceptor agonist affinity and/or receptor number. Further studies are needed in order to determine the extent and mechanism(s) underlying this phenomenon.

References

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Table 1. Number of patients (percent) and Means ± SEM.

	Group 1	Group 2
Age (years)	63.1 ± 1.3	62.8 ± 2.1
Weight (kg)	79.3 ± 1.7	80.9 ± 2.1
BSA (m^2)	1.88 ± 0.03	1.92 ± 0.04
Male/Female	62/12 (83/17)	24/2 (89/11)
Previous MI	29 (39)	17 (63) *
Beta Blockers	32 (43)	13 (48)
Nifedipine	16 (21)	8 (30)
Diltiazem	38 (51)	13(48)
Verapamil	3 (4)	1 (4)
X- Clamp (min)	67.7 ± 3.2	73.2 ± 5.8
Bypass (min)	106.7 ± 4.7	125.5 ± 10.7
Rewarming (min)	47.7 ± 1.8	55.7 ±4.8
Peak Rewarming Temperature (°C)	38.6 ± 0.13	38.8 ± 0.18
Number of Grafts	3.2 ± 0.2	3.5 ± 0.3

* $p < 0.05$ between groups

Table 2. Number of patients (percent) requiring vasoactive drug therapy during emergence from cardiopulmonary bypass.

	Group 1	Group 2
Phenylephrine	27 (36)	9 (33)
Norepinephrine	4 (5)	2 (7)
Dobutamine	9 (12)	6 (22)
Calcium	59 (79)	23 (85)
Epinephrine	4 (5)	1 (4)
Ephedrine	2 (3)	2 (7)
Dopamine	1 (1)	-
Isoproterenol	1 (1)	-
Nitroglycerin	19 (25)	6 (27)
Nitroprusside	14 (19)	4 (15)

Some patients received more than 1 drug.
There were no significant intergroup differences.

Table 3. Cardiovascular parameters (Mean ± SEM)

	a	b	c	1 Min	15 min
MAP (mmHg)					
1	94±2	64±2	70±1	72±1	80±1
2	94±2	67±2	66±2	76±2	79±2
CI (L/min)					
1	2.8±0.1	2.1±0.1	2.3±0.1	2.7±0.1	2.8±0.1
2	2.6±0.1	2.1±0.1	2.4±0.1	2.7±0.1	2.9±0.1
SVR (dyne.sec.cm^{-5})					
1	1413±47	1218±44	1186±35	1040±42	1126±39
2	1389±67	1217±58	1046±59	1074±68	1005±49
Temp (°C)					
1	36.0±0.1	24.9±0.5	36.4±0.3	37.2±0.1	36.1±0.1
2	36.2±0.1	26.0±0.6	36.6±0.5	37.5±0.2	36.6±0.1
Hct (%)					
1	40.3±0.5	24.0±0.5	24.7±0.4		27.3±0.5
2	40.2±1.0	25.0±0.6	24.5±0.6		27.0±0.6
Ca^{++} (mEq/L)					
1	1.14±0.01	1.05±0.02			1.20±0.02
2	1.15±0.01	1.04±0.03			1.19±0.04

There were no significant differences between groups

Title: DETECTION OF VENOUS AIR EMBOLISM IN DOGS WITH A CENTRAL VENOUS DOPPLER TIPPED CATHETER.

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INTRODUCTION:

Venous air embolism, an uncommon occurrence, has potentially serious consequences, such as cardiovascular collapse[1]. Early detection and treatment of venous air emboli (VAE) are considered essential to reduce the significant cardiovascular compromise. Various methods are available for detection of VAE. The most simple and sensitive method of detection of VAE is the monitoring of the precordial Doppler sounds.[2] The precordial Doppler is capable of detecting VAE in minimum volumes of 0.5 - 1.0 ml.kg^{-1}. However, the Doppler has certain limitations. It detects the VAE after the air accumulates in the right heart. Its signal to noise ratio is decreased because the structure of the chest wall attenuates this doppler signal. A miniaturized catheter tip doppler transducer system mounted on a flexible, indwelling central venous catheter was designed to overcome these problems.

This system may allow protection of VAE cephalad to the heart as the air moves through the superior vena cava. The signal to noise ratio is likely to be enhanced since the doppler transducer is in physical contact with the blood. This study was done to define the sensitivity of the doppler transducer and determine the minimal amounts of air that can be reliably detected.

METHODS:

The prototype catheter tip doppler transducer is a PZT-5 ceramic transducer designed to operate at 8.7 MHz. It is mounted circumferentially on a 16G Polyvinyl Chloride central venous catheter and coated with epoxy. This provides a low surface profile, which is smooth and electrically isolated from the blood. The doppler generator is a hand held electronic package that is rugged, battery powered and is programmable. It has output capabilities for various peripheral devices for recording. The output signal from the doppler generator was processed by a real time spectrum analyzer and displayed (Angioscan: Unigon Industries, NY). This was simultaneously confirmed by the audio signal through the earphones.

The study was approved by the Institutional Animal Care and Use Committee. Five mongrel dogs weighing 25 - 30 kg were induced with 30 mg.kg^{-1} of intravenous sodium thiopental. They were intubated and ventilation was controlled. Anesthesia was maintained with halothane in 100% oxygen with the dogs in 30 degree head-up position. An arterial catheter was placed in the femoral artery for the continuous recording of the blood pressure. A pulmonary artery catheter introducer sheath was placed in the subclavian vein. Intravenous fluid was administered at the rate of 45 ml.hr^{-1} through the side port of the introducer sheath. The prototype doppler tipped catheter was inserted through the introducer sheath and connected to the doppler generator. Its position in the superior vena cava was confirmed by fluroscopy.

VAE were introduced into the central circulation via the side port of the introducer sheath. Sequential bolus injections of 0.1, 0.25, 0.5, 1.0, 1.5, 2.0 ml were injected. Therefore, the bolus was increased by 1 ml each time till a bolus of 10 ml was injected. At least 10 minutes were allowed to pass between the injections. The "injector" who injected the air was blinded from the "detector" who detected the air and vice versa. Number of trials for each bolus of air injected were selected randomly by the injector. A total of 258 individual trials were performed in 5 experimental animals.

RESULTS:

Table 1 represents the volume of the injectate, number of injections, number of detections and the percentage of positive detections.

Table 1

Injectate Volume (ml)	Injection Trials (N)	Detection N	Positive Detection %
0	6	0	0
0.1	15	5	33
0.25	21	9	43
0.5	29	18	62
1.0	33	29	88
1.5	5	5	100
2.0	27	27	100
3.0	21	21	100
4.0	19	19	100
5.0	21	21	100
6.0	18	18	100
7.0	4	4	100
8.0	13	13	100
9.0	4	4	100
10.0	22	22	100

All VAE with volumes in excess of 1.5 ml were detected without error. The minimal volume of air that could be detected was 1.5 ml. As seen in the first column of Table 1, when no air was injected, no air was detected and hence there were no false positives. There were no discrepancies between visual signals and audio signals.

DISCUSSION:

The precordial doppler is presently the most sensitive device available for detection of VAE. It reliably detects the volume of air 0.5 - 1.0 ml.kg^{-1} body weight.[3] For our experimental animals this would be 15 - 30 mls. This study demonstrates that the catheter tip doppler consistently detected the VAE as small as 1.5 ml. This represents 0.05 - 0.06 ml.kg^{-1} body weight in these experimental animals. Thus the intravascular doppler tipped detection system is 10 - 20 times more sensitive than the precordial Doppler. This degreee of sensitivity greatly enhances signal to noise ratio. Small VAE can be detected before they have the opportunity to coalesce into a larger pocket in the right atrium. Miniaturization of the doppler generator enhances its portability which may be useful in various clinical settings.

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Title: RUBBER AND PVC ENDOTRACHEAL TUBE CUFFS ARE HIGHLY VULNERABLE TO THE CO_2 LASER

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Introduction: The shafts of combustible endotracheal tubes can be protected from the CO_2 laser by techniques such as wrapping them with the appropriate metallic foil tape.(1) However, the cuffs of these endotracheal tubes remain vulnerable to the effects of the laser. The thin and delicate nature of these cuffs suggests that they may be more susceptible to the laser's effects than the shafts of the tubes. Controversy exists as to whether the shafts of red rubber(2) (RR) or polyvinylchloride(3) (PVC) tubes are superior in their resistance to laser combustion, however no study has compared the combustibility of the cuffs of these endotracheal tubes. We evaluated the resistance of the cuffs of RR and PVC tubes to the CO_2 laser.

Methods: A LaserSonics (Santa Clara, CA) CO_2 laser's output was adjusted to 3W and a 0.68 mm beam diameter in the continuous mode of operation. Six Rusch (W. Germany) RR and six Mallinckrodt (Hi-Lo, St. Louis, MO) PVC 8.0 mm ID endotracheal tubes were studied. The endotracheal tube cuffs were placed in the necks of 250 cc Erlenmeyer flasks. After connecting the endotracheal tubes to an anesthesia circuit and flushing the tubes and flasks with 100% oxygen for 5 min, the cuffs were inflated with air to just seal at a pressure of 15 cm H_2O which was maintained within the flask and anesthesia circuit by adjusting the pop-off valve on the anesthesia machine. Using a hand held probe, the laser was aimed at the endotracheal tube cuffs. The time necessary for laser induced combustion of the endotracheal tubes was noted. The combustion times of the two groups were compared by Student's paired t-test. A level of $P<0.05$ was considered statistically significant.

Results: The CO_2 laser perforated all the endotracheal tube cuffs in less than 0.5 sec and caused a spectacular endotracheal tube fire in all cases. The flask was subsequently engulfed in black smoke. The times to combustion of the RR endotracheal tubes were 11.23 ± 11.1 (mean ± S.D.). Those for the PVC tubes were 5.57 ± 4.65. There were no statistically significant differences between these groups.

Discussion: Several studies have arrived at conflicting conclusions in attempting to show an advantage of endotracheal tubes fabricated from RR over those made of PVC for laser surgery. Patel and Hicks(2) demonstrate an advantage of RR tubes over those constructed of PVC while Wolf and Simpson(3) conclude that the PVC tubes are superior. These studies have involved only the shafts of these endotracheal tubes.

Our results demonstrated no statistically significant difference in the time to endotracheal tube combustion when CO_2 laser fire was aimed at the cuffs of PVC or RR tubes. The fact that allthe cuffs which were subjected to only 3 watts of laser radiation were quickly perforated and readily burned demonstrates the cuff's extreme susceptibility to the laser. It also shows that regardless of the composition of the cuffs, they are not adequate for laser surgery unless protected in some way. The shafts of these endotracheal tubes are not affected by such low power levels of laser fire. Patel and Hicks(2) showed that no shaft of ten RR or PVC endotracheal tubes tested with CO_2 laser set to 15 watts and a duration of 0.5 sec burned.

In a previous study Sosis(1) showed that combustible endotracheal tubes wrapped with Venture copper or 3M no. 425 aluminum foil tape could withstand 1 minute of direct exposure to the CO_2 laser operating at 70 watts with 5 L/min of oxygen flowing through the tube. Consequently, the cuff represents the most vulnerable part of a "protected" endotracheal tube during laser airway surgery.

In practice the cuffs of endotracheal tubes used for laser airway surgery should be inflated with saline rather than air. The saline should contain a small amount of methylene blue. The blue color will make laser induced perforation of the cuff more obvious and will serve as a signal to the surgeon to stop operating the laser. The saline acts as a "built in automatic sprinkler system" which will decrease the likelihood of combustion.(4) It also will serve as a heat sink that will absorb the laser's energy. As an extra line of defense, the cuff should also be packed off with wet pledgets which are kept moist. The minimal acceptable F_IO_2 as determined by pulse oximetry should be used with nitrogen or helium comprising the balance of the inspired gas mixture since nitrous oxide supports combustion to the same extent as oxygen.

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Title: **CLONIDINE DOES NOT DEPRESS THE VENTILATORY RESPONSE TO CO_2 IN MAN**

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Introduction

Clonidine has recently been evaluated as an analgesic and anesthetic agent (1,2,3). These studies demonstrate that clonidine produces antinociception and significantly decreases the requirement for other anesthetics. However, no data exists describing the effects of clonidine, either alone or in combination with other anesthetic agents on brain stem respiratory center activity in man. This study evaluated the effects of clonidine and morphine, alone and in combination, on the ventilatory and occlusion pressure responses to CO_2 in healthy young adult male volunteers.

Methods

After approval by the University of Utah Health Sciences Center Institutional Review Board, 12 young ASA Class I adult male volunteers gave oral and informed consent to participate in the study. Subjects were between the ages of 21 and 47 and weighed between 61 and 93 kg. They did not abuse tobacco or alcohol and were taking no medications. They did not eat or drink for at least 8 hr prior to study and refrained from caffeine and aspirin for 12 hr prior to each study. All studies began at 7:00 AM. Each subject was evaluated at three separate sessions at least 48 hr apart and received oral clonidine (C), 0.30 mg (60-69 kg), 0.35 mg (70-79 kg), or 0.40 mg (80-99 kg) at one session; morphine (M) 0.21 $mg{\bullet}kg^{-1}$ IM at another session; and C+M at the same doses at another session. Subjects were randomly assigned to one of the six permutations of the order in which the drugs could be administered. The study was balanced so that two subjects were assigned to each permutation. At each session, after infiltration with 0.5 cc of 1% lidocaine, a 20 g catheter was inserted into an arm vein and lactated Ringers solution infused at 125 $mL{\bullet}hr^{-1}$. Baseline ventilatory and occlusion pressure responses to CO_2 were obtained via a hyperoxic, hypercapnic technique with a computerized modified Read rebreathing apparatus. The first 10 breaths of each CO_2 challenge were eliminated from analysis to assure equilibration of CO_2. The end-tidal CO_2 increased at least 15 mmHg but not more that 25 mmHg in each subject for each CO_2 challenge. The slope of the ventilatory response (V_E/CO_2)($L{\bullet}min^{-1}{\bullet}mmHg^{-1}$), the calculated minute ventilation at an end-tidal CO_2 of 50 mmHg (V_E50) ($L{\bullet}min^{-1}$), the slope of the occlusion pressure response at 100 msec after the onset of inspiration (P_{100}/CO_2)($cm\ H_2O{\bullet}mmHg^{-1}$), and the occlusion pressure response at an end-tidal CO_2 of 50 mmHg ($P_{100}50$) were the variables selected to measure the subjects' respiratory response to CO_2 and drug effects over time. After baseline measurements were obtained, the drug(s) was administered and additional CO_2 rebreathing challenges were performed 20, 40 60, 90, 120, 180, 240, 300 and 360 min after drug administration. Statistical analysis was by repeated measurement multivariate analysis of covariance (MANCOVA) using restricted maximum likelihood estimation with a structured covariance matrix. Test statistics were Wald chi square with significance at 0.05.

Results

Ventilatory response. V_E/CO_2 (Table 1) and V_E50 were similar at baseline for all three drug groups. V_E/CO_2 and V_E50 were significantly depressed after M and M+C compared to C ($P < 0.01$; Table 1). In addition, the significant depression of V_E/CO_2 and V_E50 with C+M was no greater than M alone.

Occlusion pressure response. P_{100}/CO_2 and $P_{100}50$ were similar at baseline for all three groups. As with VE/CO2 and VE50, P_{100}/CO_2 and $P_{100}50$ were significantly depressed after M and M+C compared to C ($P < 0.01$; Table 2). In addition, the depression of P_{100}/CO_2 and $P_{100}50$ after C+M was no greater than M alone.

Table 1. V_E/CO_2 (Mean ± SEM)($L{\bullet}min^{-1}{\bullet}mmHg^{-1}$) before and after C, M and M+C

	Baseline	20 min	40 min	60 min	120 min
C	2.4±0.2	2.7±0.3	2.9±0.2	3.0±0.3	3.2±0.3
M	2.6±0.3	2.1±0.4*	1.8±0.2*	1.9±0.3*	1.6±0.2*
M+C	3.0±0.5	2.4±0.3*	2.2±0.3*	1.9±0.2*	1.8±0.2*

*P < 0.01, see methods and results

Table 2. P_{100}/CO_2 (Mean ± SEM)($cmH_2O{\bullet}mmHg^{-1}$) before and after C, M and M+C

	Baseline	20 min	40 min	60 min	120 min
C	0.49±0.08	0.55±0.08	0.50±0.07	0.55±0.07	0.63±0.09
M	0.49±0.08	0.38±0.07*	0.30±0.05*	0.28±0.05*	0.24±0.03*
M+C	0.56±0.10	0.37±0.05*	0.40±0.06*	0.33±0.05*	0.23±0.05*

*P < 0.01, see methods and results.

Discussion

To our knowledge this is the first investigation that documents an absence of significant depression of the brain stem's response to CO2 after clonidine in man. In addition, this $alpha_2$ agonist does not interact with morphine to potentiate morphine-induced respiratory depression. This has potential significance as clonidine does potentiate morphine induced analgesia (1). Thus, clonidine appears to produce analgesia, sedation and reduced anesthetic requirements as reported by others without causing significant brain stem respiratory center depression in man.

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TITLE: BIOIMPEDANCE HEMODYNAMICS COMPARED TO PULMONARY ARTERY CATHETER MONITORING DURING LIVER TRANSPLANTATION

AUTHORS: BD Spiess, M.D., KJ Tuman, M.D., RJ McCarthy, Pharm.D., AD Ivankovich, M.D.
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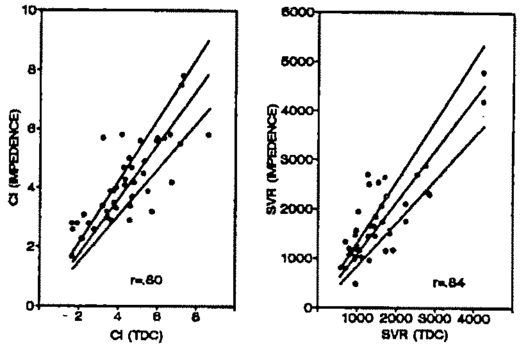
Introduction: The pulmonary artery catheter is useful for managing hemodynamically unstable patients such as those undergoing orthotopic liver transplantation (OLT). Thermodilution cardiac output (TD) determinations may be affected by rapid fluid administration which often occurs in the setting of OLT. Although continuous monitoring of mixed venous oxyhemoglobin saturation (S_vO_2) is now clinically available, changes in this measurement may not always reflect corresponding changes in cardiac output. Rapidly changing levels of hemoglobin, arterial hemoglobin saturation, and oxygen consumption commonly occur during OLT, resulting in such discrepancies. As such, alternative methods of continuously and accurately measuring cardiac output are needed in patients such as those undergoing OLT. Thoracic impedance hemodynamic monitoring (IMPED) has been shown to provide a continuous, accurate, non-invasive measurement of cardiac output during other types of surgery. In addition, bioimpedance technology allows for continuous assessment of end-diastolic volume, ejection fraction, and contractility. Because this technology is dependent only upon fluid movement in the thorax, it may not be influenced by many of the factors which interfere with PA catheter data. The purpose of this study was to compare the accuracy of IMPED and TD as measurements of cardiac index over the wide range of variation that commonly occurs during OLT.

Methods: After institutional review board approval, 10 consenting adult patients undergoing OLT were prospectively studied. Standard anesthetic and surgical management were employed in all patients, including use of femoral-portal vein to axillary vein bypass during the anhepatic phase. Thermodilution cardiac output was measured (Oximeter PA-catheter, Oximetrics, Inc., Mountain View, CA) using 10cc of room temperature injectate, and recorded as the average of at least 3 determinations which were in agreement by at least ±10%. Thoracic bioimpedance cardiac output was continuously monitored with the BoMed NCOM-3 R7 system (Bomed, Inc, Irvine, CA), using a standard array of skin patch electrodes. Simultaneous measurements of cardiac output were taken after induction of anesthesia, before and during the anhepatic phase, 10 minutes after resuscitation, and at the end of surgery. Additionally, PA pressures were measured and SVRI and LVSWI calculated. Bioimpedance measurements were averaged over the period of time used to collect thermodilution data, and included SVRI, ejection fraction (EF), index of contractility (IC), end-diastolic volume index (EDI), and acceleration contraction index (ACI). Pearson's correlation coefficients were calculated for data obtained for each of the following: CI, SVRI, pre-load (PAOP and EDI), left heart work (LVSWI and ACI, IC), and mixed venous saturation (S_vO_2 and CI-TD, CI-IMPED).

Results: Significant correlations were found between TD and IMPED for CI and SVRI (see Figure). LVSWI calculated from PA catheter data correlated significantly with IMPED-derived ACI as well as IC.

	CI-TD	CI-IMPED	EDI	ACI	IC
LVSWI	.71**	.80**	.41*	.53**	.58**
S_vO_2	.41*	.47*	.15	.10	.26

*p=.01 **p=.001



• 10% COFFIDENCE INTERVALS

The S_vO_2 was only weakly correlated with the CI determined by either method, and the PAOP did not correlate with the IMPED-derived end diastolic volume index (EDI) (r=-.06).

Discussion: The important findings of this study are that while the IMPED and TD CI measurements did correlate, some discrepancies were observed at extremes of flow. This may be due to inaccuracies in TD CI related to rapid volume infusion necessary during OLT (resulting in falsely low TD values). Conversely, because of the use of femoral-portal to axillary vein bypass in these patients, estimates of CI by IMPED may be falsely elevated since this augmentation of intrathoracic blood flow may accentuate bioimpedance changes unrelated to aortic flow. Secondly, this study demonstrates the poor correlation between S_vO_2 and CI in these patients, confirming previous data demonstrating poor correlation of S_vO_2 with either low or high cardiac indexes.(1,2) Since PAOP did not correlate with an index of end-diastolic volume (EDI), other studies are underway to confirm if the non-invaseively determined IMPED reflection of end-diastolic volume accurately trends with directly measured end-diastolic volume. In conclusion, IMPED appears to be a useful continuous, non-invasive monitor of hemodynamic function and may provide advantages because of the limitations of TD and S_vO_2 in accurately reflecting the hemodynamic profile of patients undergoing OLT.

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Title: LIDOCAINE DOES NOT ATTENUATE THE HEMODYNAMIC RESPONSE OF CHILDREN TO LARYNGOSCOPY

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Introduction: The pharmacological modification of the sympathetic response to laryngoscopy and tracheal intubation is well documented [1-3]. Most, if not all, of the investigations of the pressor response involved adults. Children are also at risk of developing complications secondary to an excessive sympathetic response. Previous investigations of healthy adults demonstrated that intravenous lidocaine decreased the hemodynamic responses during induction, but this beneficial effect was only observed if lidocaine was administered 3 minutes before laryngoscopy [1]. We sought to determine: 1. whether 1.5 mg/kg[1] of intravenous lidocaine attenuates the pressor response of children, and 2. the optimal time to administer lidocaine prior to laryngoscopy and tracheal intubation.

Methods: After Hospital Ethics Committee Approval and informed, parental consent, 125 elective, ASA I-II surgical patients of age 2 to 12 years were randomly assigned to one of five groups. Children were excluded for several factors, including treatment with sympatholytic drugs, an active seizure disorder, gastro-esophageal reflux, and renal or hepatic dysfunction. **Baseline values:** On arrival in the operating room the patient's heart rate (HR), systolic blood pressure (SBP), mean blood pressure (MBP), and diastolic blood pressure (DBP) were measured with a Dinamapp R automatic non-invasive blood pressure (NIBP) monitor. The average of the first two values, which were obtained one minute apart, constituted the baseline value. **Induction:** After breathing a mixture of 70% N_2O and 30% O_2 for 1 minute an intravenous catheter was inserted. 100% O_2 was given for the remaining 4 minutes of the induction period. During induction the patient's hemodynamics were measured every minute with the NIBP unit. The final values were obtained 2 minutes after tracheal intubation. Four groups of 25 patients were administered lidocaine IV (1.5 mg/kg) either 1, 2, 3 or 4 minutes before laryngoscopy and intubation. The remaining 25 patients were in the control group and thus did not receive lidocaine. Vecuronium (0.08 mg/kg) and thiopentone (6 mg/kg) were administered 1.9 minutes and 1.7 minutes prior to intubation, respectively. Intubation was performed within 15 seconds. After intubation, anesthesia was maintained for the next 2 minutes with 70% N_2O, 30% O_2 and 1.5% halothane delivered through a coaxial circuit and controlled ventilation was established to maintain normocapnia. Patients were not stimulated during the observation period (from the start of the induction to 2 minutes after intubation). Data were compared using ANOVA, Kruskal-Wallis ANOVA, repeated-measures ANOVA and ANCOVA, where appropriate. All results were accepted as significant if $P < 0.05$.

Results: There were no significant differences between the groups' weight, age, gender and ASA class. Lidocaine treatment neither eliminated nor attenuated the induction pressor response (Figure). Hemodynamic responses to laryngoscopy had peaked by 1 minute after tracheal intubation and were different than baseline values (repeated-measures ANOVA). By 2 minutes after intubation, all the values had returned to baseline. Between group comparison of the 1 minute post-intubation HR, SBP, DBP and MBP did not identify any significant differences between the groups (ANCOVA). By ANCOVA, the HR and SBP 1 minute after intubation was significantly modified by baseline HR and SBP ($P < 0.05$). Specifically, a higher baseline HR or SBP resulted in greater pressor response. Older subjects had a greater hemodynamic response (SBP and MBP) to laryngoscopy and intubation than younger patients (ANCOVA $P < 0.05$).

Discussion: Hemodynamic stability during induction is a major objective in anesthesia. In young adults the optimal time to administer IV lidocaine before intubation is approximately 3 minutes.[1] Lidocaine given 1, 2 and 5 minutes before intubation had no beneficial effect.[1] This study of children was unable to demonstrate a significant effect of lidocaine on induction hemodynamic variables if given 1, 2, 3 or 4 minutes before tracheal intubation. Theoretically, lidocaine should decrease MAC and obtund the laryngeal reflexes of children and thus attenuate the pressor response.

This study compared post-intubation hemodynamic variables using ANCOVA. This form of analysis appropriately weighs the effect of the baseline value, the effect of the subject's age on hemodynamic responses and the effect of the study medication administered to alter this response. Not only does the average blood pressure and HR vary with age, but we were able to demonstrate that the hemodynamic response (MBP and SBP) was significantly altered by the age of the subjects studied.

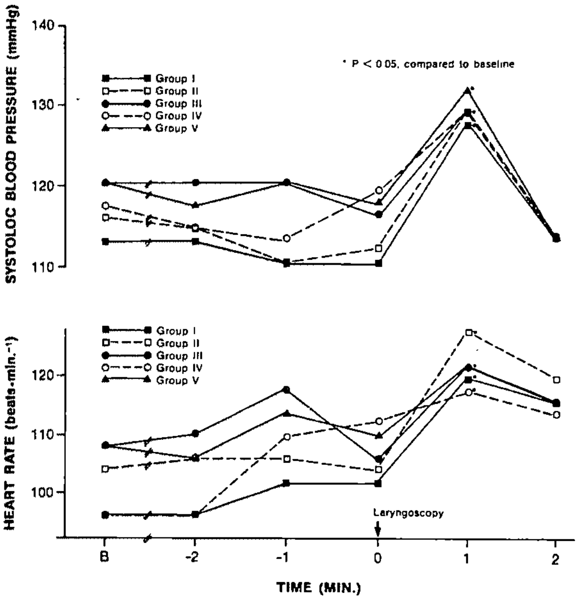

Figure. The heart rate and systolic blood pressure at rest (time = B, operating room baseline), during induction of anesthesia, and before and after tracheal intubation in patients treated with thiopentone only (Group V), and in combination with lidocaine 1, 2, 3 and 4 minutes before laryngoscopy, Groups I-IV, respectively.

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Title: A 2-HOUR CLEAR FLUID FAST IS SAFE FOR CHILDREN

Authors: WM Splinter,MD,FRCP(C), JD Schaefer, MD, FRCS(C), IH Zunder, MD

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Introduction: The most suitable length of time to restrict clear fluid ingestion by children before elective surgery is unknown. Recent investigations have established the safety and potential benefits of administering preset volumes and types of clear fluids to children and adults on the day of surgery.[1-3] We hypothesized that children of ages 2 to 12 years could safely ingest unrestricted volumes and types of clear aqueous fluids up to 2.5 and 2 hours before elective surgery.

Methods: Following Hospital Ethics Committee Approval and with parental informed consent, 228 healthy (ASA physical status 1 or 2) children, ages 2-12 years, scheduled for elective surgery were randomly assigned to different fasting guidelines. Patients were excluded fromthe study if there was a history of intestinal disease or if the patient's medication was known to affect gastric contents.

Following our usual practice, the patients were asked to abstain from solid food after midnight. During the first phase of this study, 80 patients were evenly divided between 2 groups of patients. The first group of 40 patients were allowed to have clear fluids up to 3 hours before their operation and the second group were permitted to ingest clear fluids up to 2.5 hours before their anesthetic. During the second phase of the study, 74 patients were allowed clear fluids up to 3 hours before surgery, and 74 patients ingested clear fluids up to 2 hours before their operation.

After the establishment of an adequate and stable level of anesthesia, a 14 or 16 Fr. Levin^{R} gastric tube was passed orally into the stomach by a blinded investigator. The position of the gastric tube was confirmed by auscultation; the stomach contents were aspirated with the gastric tube and patient in several positions. Gastric contents were visually inspected for particles and color. Volume was measured with a syringe and the gastric pH was estimated using pH paper (Merck pH 0-14 and pH 0-2.5). Gastric volumes less than 1 ml were approximated the value of 0.5. Data was analyzed using Student's t test, Mann-Whitney-U test, chi-square analysis, and Fisher's exact test and the potential relationships between gastric volume or gastric pH and gender, age, weight and length of fast by linear regression analysis. Values were considered to be significantly different if $p < 0.05$.

Results: There were no significant differences between the groups with respect to age, gender, ASA physical status, in-patient/out-patient status and weight. There was no significant difference between the groups with respect to gastric volume aspirated and gastric pH (Table I). The groups of children did not have increased incidence of gastric volumes greater than 0.4 ml/kg and pH less than 2.5 (Table II). The children ingested 250 ± 100 ml. on the day of surgery (Table III). Gastric volume (ml/kg) increased as age and weight increased ($P < 0.0001$).

TABLE I- GASTRIC CONTENTS

Group	n	Volume (ml/kg) mean ± SD (range)	pH mean ± SD (range)
Phase I			
3.0 hr. fast	40	0.38±0.30 (0.02-1.31)	1.8±0.9 (1.2-7.0)
2.5 hr. fast	40	0.37±0.37 (0.02-1.54)	1.9±1.0 (1.2-7.0)
Phase II			
3.0 hr. fast	74	0.27±0.30 (0.02-1.81)	1.9±1.0 (1.2-6.0)
2.0 hr. fast	74	0.33±0.49 (0.02-2.81)	1.8±1.0 (1.3-7.0)

TABLE II-LARGE VOLUME GASTRIC CONTENTS

Group	n	Volume > 0.4 ml/kg and pH < 2.5	Volume >1.0
3.0 hr. fast	40	18/40	2/40
2.5 hr. fast	40	13/40	2/40
Phase II			
3 hr. fast	74	19/74	2/74
2 hr. fast	74	13/74	5/74

TABLE III-VOLUME INGESTED AND FAST

Group	Volume Ingested (ml/kg) mean ± SD (range)	Fast (hr.) mean ± SD (range)
Phase I		
3.0 hr. fast	11 ± 8 (1-34)	3.5 ± 0.9 (2.2 -6.0)
2.5 hr. fast	9 ± 7 (1 - 39)	2.9 ± 0.9 (1.8 - 5.5)
Phase II		
3.0 hr. fast	12 ± 9 (1 - 65)	3.5 ± 0.7 (2.3 - 6.0)
2.0 hr. fast	14 ± 10 (2 - 50)	2.5 ± 0.9 (1.1 - 6.0)

Discussion: Based upon these results, children, who are without factors which may lead to increased gastric contents, may safely ingest unrestricted clear fluids up to 2 hours before they are administered an anesthetic.

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Title:
UNRESTRICTED CLEAR FLUID INGESTION 3-HOURS BEFORE ANESTHESIA IS SAFE FOR ADOLESCENTS

Authors: WM Splinter MD, FRCP(C), ME Schneider, MD, JD Schaefer, MD, FRCS(C)

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Introduction: Patients are normally required to abstain from food and drink before the induction of anesthesia in order to keep gastric contents to a minimum. The appropriate time and the benefits of restricting clear fluid ingestion by adolescents is not clearly established. Recent investigations have demonstrated the safety of administering preset volumes and types of clear fluids to children and adults on the day of surgery.[1-3] We hypothesized that adolescent could safely and beneficially ingest unrestricted volumes and types of clear aqueous fluids up to 3 hours prior to elective surgery.

Methods: Following Hospital Ethics Committee approval and with the parental or patient informed consent, 108 healthy (ASA physical status 1 or 2) adolescents, ages 13-19 years, scheduled for elective surgery were randomly assigned to one of two groups. Patients were excluded from study, if there was a history of gastrointestinal disease or if the patient's medication was known to affect gastric contents.

Following our usual practice, the patients were asked to fast after midnight. Fifty-eight adolescents remained in a state of starvation and fifty were allowed to have unrestricted clear fluids up until 3 hours prior to their scheduled operation. In the operating room waiting area, the patients were asked to complete a questionnaire concerning their hunger and thirst (linear analogue scale from 0 to 10 with 0 corresponding to no thirst or no hunger).

After establishing an adequate and stable level of anesthesia, a 14 or 16 Fr. Levin^R gastric tube was passed orally into the stomach by a blinded investigator. The position of the gastric tube was confirmed by auscultation and the stomach contents were aspirated with the gastric tube in several positions and the patient tilted to the right, left, head-down and head-up positions. Gastric contents were visually inspected for particles. Gastric volume was measured with a syringe and gastric pH was estimated using pH paper (Merck pH 0-14 and pH 0-2.5). Gastric volumes less than 1 ml were approximated the value of 0.5 ml. Normally-distributed data was analyzed using Student's t test, non-parametric data was analyzed with Mann-Whitney-U test, chi-squire analysis, and Fisher's exact test and the potential relationships between gastric volume or gastric pH and gender, age, weight and length of fast by linear regression analysis. Values were considered to be significantly different if $p < 0.05$.

Results: There were no significant differences between the groups with respect to age, gender, ASA physical status, in-patient/out-patient status and weight. Adolescents allowed clear fluid ingested 260 ± 170 ml on the day of surgery and ingested fluids up to 3.6 ± 0.7 hours before surgery. There was no significant difference between the groups with respect to gastric volume aspirated and gastric pH (Table I). Adolescents who ingested unrestricted clear fluids on their day of surgery, did not have increased incidence of gastric volumes greater than 0.4 ml/kg and pH less than 2.5 (Table II). The difference between the patient's assessment of thirst and hunger was not different (Table III).

TABLE I-GASTRIC CONTENTS

Group	Volume (ml/kg) mean ± SD (range)	pH mean ± SD (range)
3 hr. fast	0.45 ± 0.40 (0.02 -1.47)	1.9 ± 1.2 (1.2 - 6.5)
Overnight fast	0.46 ± 0.42 (0.02 - 2.11)	1.6 ± 0.4 (1.3 - 3.0)

TABLE II-LARGE VOLUME GASTRIC CONTENTS

Group	n	Volume > 0.4 ml/kg and pH < 2.5	Volume > 1.0 ml/kg
3 hr. fast	50	21/50	7/50
Overnight fast	58	25/58	7/58

TABLE III-PATIENT THIRST AND HUNGER

Group	Thirst mean ± SD	Hunger mean ± SD
3 hr. fast	4.1 ± 2.4	6.0 ± 2.5
Overnight fast	5.0 ± 2.7	5.9 ± 2.7

Discussion: Based upon these results, we permit adolescents, who are without 'risk' factors of increased gastric contents, unrestricted clear fluids up to 3 hours before they are administered an anesthetic for elective surgery.

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MECHANISM PRODUCING RESPIRATORY INSUFFICIENCY AFTER UPPER ABDOMINAL SURGERY: PAIN VS. DIAPHRAGM DYSFUNCTION (HUMAN AND DOG STUDY)

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Introduction Decreases in forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), and functional residual capacity (FRC) invariably occur after upper abdominal surgery (UAS). This may result in postoperative hypoxemia. Among the possible etiologies of postoperative ventilatory dysfunction are surgical site[1], pain and muscle splinting[2], and diaphragm dysfunction[3]. This study was designed to determine the contribution of pain and diaphragmatic dysfunction to postoperative pulmonary compromise.

Methods Part I: After approval by the institutional review board and informed consent obtained, the role of postoperative analgesia on preserving respiratory function was evaluated on 16 patients after UAS receiving analgesia by the epidural route or PCA. The degree of postoperative pain control was assessed with visual analog pain scale (VAS). Respiratory function was evaluated by measuring FVC, FEV_1, SpO_2, and RR preoperatively and for three days after surgery.

Part II: Diaphragm function after UAS was investigated in a dog model. Four anesthetized beagle dogs had an upper abdominal laparotomy. The left hemidiaphragm was exposed and 4-6 lead markers were sutured in a row fashion along diaphragm muscle bundles in four regions: left crural (Cr) and ventral (CoV), middle (CoM) and costal dorsal (CoD) diaphragm. The overall length of marker rows, measured as a cumulative sum of all intermarker distances, represents the regional muscle length. Diaphragm shortening was studied during spontaneous breaths by biplane-videoroentgenography[5]. Results were expressed as a relative shortening from the respective regional length at FRC (%ΔL FRC) on the day of surgery, 3rd, 15th, and 30th postoperative day.

Statistics: All data were expressed as mean ±SD and compared by ANOVA and Bonferroni tests, except SpO_2 by paired t-test. Accepted level of statistical significance was $p < 0.05$.

Results Mean postoperative VAS for epidural opiates and PCA was 3.2±7. Patients with VAS scores ≤3 are considered as having good analgesia. Preoperative and postoperative RR (17.8±0.7/19.3±1.2) were not different. Preoperative SpO_2 was significantly different from postoperative values on POD #1 (98±0.9/95±3.6). Both groups showed parallel decrease in FVC and FEV_1 ($p < 0.001$) by approximately 47% on POD #1 which persisted until POD #3 (Fig. 1). Regional diaphragm shortening is diminished in all four regions during the immediate postoperative period (Fig. 2). Some regions showed paradoxical lengthening with inspiration which is consistent with muscle paralysis (Fig. 3, data from one dog). There is significant improvement in diaphragm shortening by POD #3. After, POD #15 diaphragm function was not significantly different from POD #30 which was considered normal(Fig. 2).

Discussion Respiratory pattern in postoperative period after UAS is restrictive in nature. Failure to reverse diminished respiratory function with effective pain control suggests that muscle splinting from pain plays only a minor role in postoperative respiratory insufficiency. Direct measurement of diaphragm shortening showed immediate postoperative diaphragm hypocontractility. The decreased shortening and even areas of diaphragm paralysis provoked by UAS suggest acute injury to the diaphragm. Increased diaphragm contractility as demonstrated by improved shortening may take as long as 15 days to normalize. As the regional lung ventilation is closely coupled with active diaphragm displacement, diaphragm behavior in the immediate postoperative period is consistent with hypoventilation, increased V/Q mismatching and the development of atelectasis. This study demonstrates that pain control has a limited effect on improving respiratory function and that diaphragm dysfunction is the major etiologic factor in postoperative ventilatory insufficiency.

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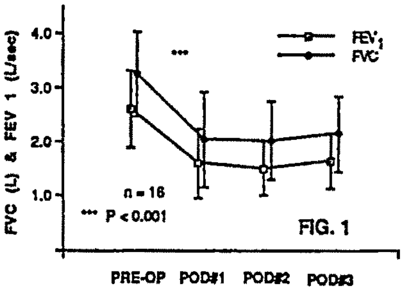

FIG. 1

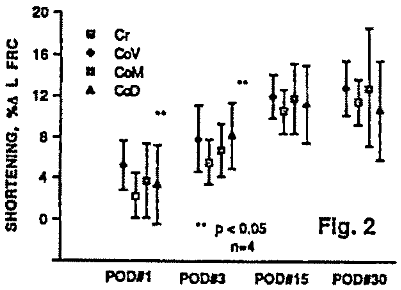

Fig. 2

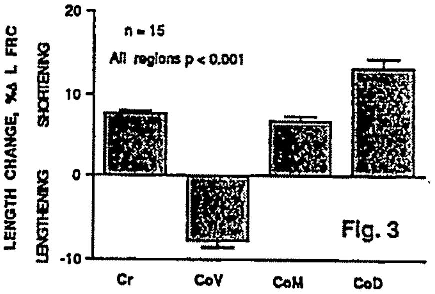

Fig. 3

Title: A RELIABLE METHOD FOR THE ASSESSMENT OF THE END POINT OF RECOVERY FROM RESIDUAL NEUROMUSCULAR BLOCK

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Introduction. The end-point of full recovery from neuromuscular block has yet to be established. Presently, as many objective criteria as practical are utilized to correlate with the clinical criteria of recovery from neuromuscular block. In partially curarized patients, the enhancement of the posttetanic muscle response occurs and is known as posttetanic facilitation (1,2). Yet, in the absence of a muscle relaxant, posttetanic facilitation is not observed following 50 Hz tetanic stimulation (3). This study evaluated the suitability of using the posttetanic facilitation of the train of four (PTF-TOF) after 50 Hz tetanic stimulation as a means for determining the full recovery from neuromuscular block.

Methods. Twenty healthy adults of either sex were studied during elective orthopedic procedures. Institutional Board Review approval was secured. Informed consent was not obtained since the anesthetic technique was one that is commonly used and neuromuscular function is routinely monitored at this institution. Anesthesia was induced with sodium thiopental, 3-5 mg/kg, and fentanyl, 2 ug/kg, and maintained with a 4:2 L/min N_2O-O_2 mixture supplemented with incremental doses of fentanyl. The intubating dose of vecuronium was 0.1 mg/kg and incremental doses were given as required to maintain neuromuscular block. Ventilation was controlled. Neuromuscular function was measured by using a Professional Instruments Myotrace and recording the contractile responses of the adductor pollicis muscle evoked by stimulation of the ulnar nerve at the wrist. The train of four (TOF) stimuli were continuously applied as supramaximal rectangular pulses of 0.2 msec duration and repeated every 10 sec except when interrupted for tetanic stimulation at 50 Hz for 10 sec. Tetanic stimulation was always given 10 sec after the last TOF. Tetanic stimulations were at least 3 min apart. The output from the Myotrace was displayed on a Datascope 2000 monitor and recorded on a Datascope 2000 R annotating recorder. Control measurements of the TOF and tetanic stimulation were obtained prior to the administration of vecuronium. The first posttetanic TOF stimulation was always delivered 5 sec from the end of the tetanic stimulation. At the end of surgery, when neuromuscular function was partially recovered, the following parameters were quantitated: the peak tension of the first response in TOF train (T1), the ratio of the last and first responses in the TOF train (T4/T1) and the ratio of the peak posttetanic tension in the TOF responses to that of the control pretetanic peak TOF tension.

Results. The mean and range in weight and age of the patient were respectively 76 kg, 46-98 kg, and 42 yr, 21-59 yr. Eleven were males and 9 were females. At the end of surgery and during the recovery from neuromuscular block, when transmission was only partially present, the TOF responses immediately following the 50 Hz stimulation were greater than the responses before the tetanic stimulation. The first 2 to 10 TOF responses demonstrated this phenomenon, which was the posttetanic facilitation of the TOF (PTF-TOF). The response of the very first posttetanic TOF always had the greatest facilitation. As the T1 returned to control and the T4/T1 ratio approached 1, PTF-TOF also returned to control. No clinical signs of residual neuromuscular block were observed in the operating or recovery rooms.

Discussion. The major finding of this study is that the PTF-TOF is a reliable indicator of the presence of residual block. Consequently, its absence indicates the full recovery of neuromuscular transmission. The PTF-TOF appears to be a similar phenomenon to the posttetanic facilitation of the twitch responses and is easily observed after the conditioning 50 Hz tetanic stimulation in the presence of residual block. Viby-Mogensen and coworkers have developed the posttetanic count method for evaluating intense neuromuscular block (4). Another area in which the evaluation of neuromuscular transmission is extremely important is during recovery. Evidently, the TOF does not fully meet this need. The neuromuscular junction apparently needs to be greatly stressed to show residual block. Thus, techniques which involve tetanic stimulation are being investigated (5). When the muscle tension is being measured, the tension of the tetanic response is much greater than the TOF response and could be at the ceiling of the transducer. If this were the case, little or no tetanic fade would be seen. The use of the PTF-TOF avoids this difficulty since it identifies the after effects of tetanic stimulation.

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Title: THE RECOVERY FROM RESIDUAL NEUROMUSCULAR BLOCK IN SURGICAL OUTPATIENTS

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Introduction. Due to their shorter duration of action, both atracurium and vecuronium, are the drugs of choice in same day surgical procedures. Recently, we had designed a reliable method for the assessment of residual neuromuscular block. Using this technique, the posttetanic facilitation of the train of four (PTF-TOF), the present study evaluated the recovery from residual neuromuscular block produced by atracurium and vecuronium in same day surgical patients.

Methods. Institutional Board Review approval was secured. Informed consent was not obtained since the anesthetic technique is one commonly used and neuromuscular function is routinely monitored at our institution. Forty ASA I and II patients were studied during elective outpatient procedures of 30-60 min duration requiring endotracheal intubation. Patients were randomly assigned to two groups of twenty: one received atracurium and the other vecuronium. Anesthesia was induced with sodium thiopental, 3-5 mg/kg, and fentanyl, 2 ug/kg, and maintained with a 4:2 L/min N_2O- O_2 mixture supplemented with incremental doses of fentanyl. The endotracheal intubation was accomplished with atracurium, 0.5 mg/kg, or vecuronium, 0.1 mg/kg. Additional doses of atracurium or vecuronium were given as needed to maintain adequate neuromuscular block. Neuromuscular function was measured by using a Professional Instruments Myotrace and recording the contractile responses of the adductor pollicis muscle evoked by supramaximal stimulation of the ulnar nerve at the wrist via a pair of non-invasive skin electrodes using a constant current nerve stimulator. Train-of-four (TOF) stimuli were applied as rectangular pulses of 0.2 msec duration at 0.5 sec intervals and repeated every 10 sec except when interrupted for tetanic stimulation at 50 Hz for 10 sec. The output from the force transducer was displayed on a Datascope 2000 monitor and recorded on a Datascope 2000 R recorder. During recovery from neuromuscular block, the posttetanic facilitation of the train of four (PTF-TOF), and both TOF and tetanic fade were quantitated. All patients were also clinically evaluated for residual block.

Results. Both patient groups had a similar age, sex and weight distribution. In the absence of muscle relaxants: the mean peak tension of the first muscle response in TOF was 1.8 kg ± 0.6 (SD); the mean peak tetanic tension was 7.3 kg ± 1.9; and at 50 Hz tetanic tensions were maintained. No PTF-TOF was observed during the control period. When neuromuscular block was partially recovered, the TOF responses following the 50 Hz stimulation were enhanced when compared to the pretetanic TOF responses. The criteria used for assessment of full recovery included the return to control values of the evoked responses of the peak tension of the first muscle response in TOF, the peak tetanic tension, tetanic fade ratio and the absence of PTF-TOF. When the TOF ratio $\geq$ 0.9, little PTF-TOF developed after the 50 Hz tetanic conditioning. PTF-TOF was considered to have returned to control when PTF was $\leq$ 5%. When this occurred, in the vecuronium and atracurium patients respectively, the mean peak tensions of the first muscle responses in TOF were 1.7 kg ± 0.6 and 1.8 kg ±0.7; the mean peak tetanic tensions were 7.1 kg ± 2.0 and 7.2 kg ±1.9, and tetanic tensions were maintained. Using the disappearance of the PTF-TOF as the criterion for the assessment of full recovery from residual neuromuscular block correlated well with the clinical evaluation of full recovery. If the spontaneous recovery of TOF ratio was < 0.8, edrophonium 0.5 mg/kg with atropine 0.007 mg/kg was administered. A high incidence of complete spontaneous recovery from neuromuscular blockade was observed. A major difference between the atracurium and vecuronium groups was the need for reversal of neuromuscular blockade. Reversal was required in 50% of those recovering from vecuronium and only in 10% of those recovering from atracurium. The atracurium patients who had complete spontaneous recovery of neuromuscular function showed an impressive coordinated mobility. Early ambulation was observed with both groups.

Discussion. PTF-TOF has also been described as posttetanic potentiation (PTP) or as a transient frequency dependent posttetanic decurarization. PTP is used to diagnose the presence of non-depolarizing muscle relaxants. We now have demonstrated that PTF-TOF can be used as an indicator of residual neuromuscular block and its absence as the end point of recovery. Currently at this institution, the number of same day surgical procedures are increasing. In those cases where muscle relaxants are used, it is important that no residual neuromuscular block exist. A current criterion for the return of neuromuscular function is a T4/T1 ratio $\geq$0.7. It is difficult to determine this value by tactile or visual means and a ratio of 0.7 may not detect residual neuromuscular block (1,2). The development of PTF-TOF indicates the presence of residual neuromuscular block. When the T4/T1 ratio $\geq$0.9 , little or no PTF-TOF occurs. This strongly suggests that when testing for residual neuromuscular block, the T4/T1 ratio should be $\geq$0.9. Another interesting finding was the higher percentage of patients with complete spontaneous recovery from atracurium which suggests that this agent may be the drug of choice in surgical outpatients. In summary, our search for a simple but reliable test during routine monitoring of non-depolarizing muscle relaxants has found PTF-TOF to be a reproducible and reliable phenomenon in assessing the recovery from residual neuromuscular block. The return of PTF-TOF to control values coincided with T4/T1 ratio values $\geq$0.9. The excellent spontaneous or induced recovery of neuromuscular function in surgical outpatients makes both atracurium and vecuronium highly suitable for outpatient procedures.

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Title: SIGNIFICANT BACTERIAL COLONIZATION OCCURS ON THE SURFACE OF NON-DISPOSABLE SPHYGMOMANOMETER CUFFS AND RE-USED DISPOSABLE CUFFS:

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Introduction. This study investigated the possibility that significant bacterial contamination of re-usable, non-disposable blood pressure cuffs might occur in the operating room, P.A.C.U., and I.C.U. settings. Such contamination might be of clinical significance were the BP cuff to be located in the region of the operative site during a surgical procedure, or near a wound in the post-operative period. Colonization might be of greater significance in the case of immunosuppressed, obstetric, and orthopaedic patients undergoing total joint replacement because of the increased need for sterility. Previous studies had pointed out that blood pressure cuffs could indeed be a vector for the transmission of bacterial infections in ward and ICU settings (1,3). A comparison of the relative colonization of re-used cuffs of both permanent and disposable types used with manometers and non-invasive automatic blood pressure moniters was made with clean, disposable cuffs.

Methods. Blood pressure cuffs for study were obtained from the operating rooms and ICU settings at three institutions; a university hospital, an orthopaedic hospital, and a cancer-center hospital. Cuffs were cultured within their utilization site and were all "clean" and ready for patient use. Cultures were taken at different times of the day, so as to avoid a possible bias of cuffs being cleaned at the end of the day. Cuff cultures were coded so that microbiologic technicians were unaware of their source. Actual cultures were obtained using Rodak trypticase soy agar plates, which were directly applied to the surface of the cuffs on inner and outer surfaces, since both are potentially contaminable and thereby potentially communicable. Plates were sealed, incubated at 37 degrees, and read out at 48 and 72 hours by a chief microbiologist technician at one institution. Results included both a colony count and identification of organisms cultured. Antibiotic sensitivities were obtained on pathogenic organisms.

Results. In a data collection group of 80 separate patient-related cultures, the colonization rate was 98.7% ($p<0.001$). In order to assess the significance of the degree of colonization, six anesthesiologist's medial upper arms were cultured directly, and significance was thus defined as a colony count greater than the mean colonization rate of the samples thus obtained, i.e. >20 colonies/16 cm^2. 85% of all patient-related cultures had 'significant' bacterial colonization.

30 % of all patient related cultures (N=80) had an organism other than a coagulase negative staph. growing. All organisms were suseptible to antibiotics and none were methicillin resistant. Of assays obtained from an orthopaedic hospital (N=17), 100 % of cuffs were colonized, with significant colonization of 71%. Samples obtained at the end of an operative day, after the O.R.'s were cleaned and closed, including a wiping of cuffs, produced lower colony counts in the orthopaedic hospital, with a significant colonization of 50% (N=6). Of assays obtained from a cancer-center hospital (N=23) with a large percentage of immunosupressed patients, 100 % of the cuffs were colonized, with significant colonization of 80%. The most common organism cultured overall was coagulase negative staphylococci (Staph. Epi.), growing off of 79 of 80 cuffs. Thirteen cultures obtained at the cancer hospital came from disposable cuffs which were being re-used until they appeared to be dirty, and twelve of these(92%) produced significant colonization.

Highest rates of colonization were generally obatined from cuffs used in P.A.C.U.-I.C.U. settings.

The only negative significant colonizations that were consistently observed were derived from cultures of new, non-used, disposable blood pressure cuffs(N=4).

Discussion. The study showed that 'significant' bacterial colonization of blood pressure cuffs utilized in the O.R., I.C.U. and P.A.C.U. settings does occur. Cuff types surveyed included automatic and manometric types of the permanent and disposable types. Cuff materials were either nylon or plastic. Previous studies have shown that blood pressure cuffs can actually be a clinically important vector in the transmission of infection on an in-patient floor (1), and in a neonatal I.C.U.(3).

Attitudes of staff employing the cuffs, including anesthesiologists and nursing professionals were also informally surveyed, and revealed that almost none routinely cleaned cuffs between patients, and few regarded the cuff as a possible source for infection.

It is thus recommended that efforts be made to reduce bacterial contamination of blood pressure cuffs. Cuffs should be located on the contralateral limb to the operative site when at all possible. Spraying cuffs with a topical disinfectant such as chlorhexidine can reduce their bacterial load by 75% (2,4). Repeated use of a disposable cuff on different patients produces significant colonization on the cuffs, and defeats their major advantage. Only clean, non-used disposable cuffs had insignificant colonization rates in this study. Ideally , it is recommended that where applicable, a cleansed cuff, or an unused disposable cuff be dedicated to a patient upon arrival to the hospital, and that it follow the patient to the O.R., to the P.A.C.U., and to the floor. This can also be adopted in I.C.U. settings. Such a procedure has been associated with a threefold reduction in nosocomial infection rate in a I.C.U. setting (3). Further studies are underway to quantify colonization rates on patient's skin directly, pre and post-operatively following application of a re-usable blood pressure cuff in the O.R.. It is hoped that these results and safeguards might further reduce the risks and improve the care of patients in the operating room, P.A.C.U., and I.C.U. settings.

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Title: ANESTHESIA PERSONNEL: HIV KNOWLEDGE AND PRECAUTIONS

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INTRODUCTION: Potential exposure to and subsequent infection with the Human Immunodeficiency Virus (HIV) is a risk facing the practicing anesthesiologist; a risk that will increase considerably over the next few years. Recent statistics estimate that between 1 and 1.5 million individuals in the United States are already infected with HIV.[1] The purpose of our investigation was to determine, by questionnaire and observation, what precautions members of our department were taking to prevent transmission of the HIV to themselves, and their patients. We wished to compare the precautions exercised versus those recommended by the Center for Disease Control (CDC). We also wanted to ascertain if age, clinical experience, or general knowledge about the HIV affected the precautions taken, and if previous personal or professional HIV exposure influenced the precautions exercised.

METHODS: The investigation was divided into two phases. During phase I, personnel were unobtrusively observed specifically for their use of infectious disease precautions. We recorded their use of gloves, masks, eye protection and gowns during tracheal intubation, nasogastric tube placement/removal, tracheal sectioning, vascular catheterizations, administration of blood products, cardiopulmonary resuscitations, and emergency room resuscitations. We also recorded whether needles were recapped, and where the uncleaned laryngoscope was placed following intubation. We used the published recommendations of the CDC to determine what precautions should be observed. Since masks are routinely worn in the operating theater, observations and questions related to the use of masks were only evaluated in other clinical areas. Individuals who routinely wore prescription eyeglasses were asked to skip the eyeware protection sections of the questionnaire. After preliminary observations, a survey questionnaire was distributed to personnel during a weekly conference. The questions included in the survey were those we thought appropriate to assess the knowledge base of a practicing anesthesiologist. The respondents were shown a twenty minute videotape about the care of HIV antibody positive and AIDS patients. In addition, institutional guidelines with specific precautions were distributed. The tape was followed by a review of the knowledge questions and their correct response. Two months later (Phase II), the questionnaire was redistributed and follow-up observations were made. Responses to the questions were made along a five point frequency scale. Individual practices were ranged from never to always. Respondents were partitioned into three groups according to individual practices: adequate, inadequate, or excessive. The responses to the questions and the observed practices were analyzed using frequency distribution calculations, chi square tests, and Pearson's correlation coefficient where appropriate.

RESULTS: Our survey revealed adequate precautions were employed less than 50% of the time, while individuals performed routine procedures. Direct observation confirmed that inadequate precautions were taken by the majority of practitioners. Statistically significant positive correlations were found between years of clinical practice and precautions taken while inserting vascular catheters ($\alpha<.05$), performing endotracheal sectioning ($\alpha<.05$), and negative correlation with handling the laryngoscope ($\alpha<.05$) Overall, the group exhibited limited knowledge regarding HIV. A negative correlation was identified between knowledge and precautions taken for several procedures. More precautions were taken when caring for known HIV positive and high-risk patients. Post-education survey analysis demonstrated a significant increase only in the use of gloves during routine procedures. Knowledge scores showed slight improvement, which were limited to the isolation of HIV in fluids and high risk patient groups.

DISCUSSION: We discovered that anesthesia personnel were not taking adequate precautions to protect themselves or their patients from unnecessary HIV exposure. General knowledge about HIV was limited, however, this did not reflect significantly on individual practices. Marginal benefits were obtained from additional education about the HIV. The close correlation between survey results and observational data suggests that reliable, accurate information about clinical practices can be obtained from a questionnaire. Limited alteration of practices after education may reflect little change in attitudes about HIV, indicating marginal benefits from additional education. Rules and guidelines may be required to facilitate the use of adequate precautionary measures by anesthesia personnel.

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TITLE: METABOLIC RATHER THAN MECHANICAL STRESS OCCURS DURING HEART FAILURE AND SPONTANEOUS VENTILATION IN PIGS.

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INTRODUCTION. This study examined how moderate and severe acute heart failure influenced lung mechanics and O_2 consumption (VO_2) during spontaneous ventilation.

METHODS. After institutional approval for this investigation was granted, 14 pigs were sedated, tracheally intubated, and then anesthetized with pentobarbital. They were monitored with an arterial catheter, a pulmonary artery thermodilution catheter and intrapleural and airway catheters. They breathed spontaneously through a water-sealed spirometer containing 100% O_2 for at least 10 minutes after monitor placement. Control data were obtained only if no primary respiratory acidemia existed. After obtaining measurements during normal cardiac output (CO), esmolol moderately and then severely depressed cardiac output.[1] Moderate heart failure was defined by an O_2 extraction ratio (O_2ex) of 35%; severe heart failure by O_2ex of 50%. Pigs breathed spontaneously for 20 minutes during each state prior to data collection. Standard equations for lung compliance (C_L), elastic work of breathing (Wel), respiratory power (P_R), and O_2 delivery (O_2del) were used. VO_2 and tidal volume were obtained from water-sealed spirometer tracings. Gas volumes from the spirometer were corrected to body temperature. A repeated-measure analysis of variance determined if variables differed between states.

RESULTS. Pulmonary artery temperatures did not vary more than .5°C during the study period for any pig. Esmolol infusion predictably depressed cardiac function (Table 1). Blood gas and pH values reflected normoventilation and unchanged arterial oxygenation during moderate heart failure. With severe heart failure, arterial oxygenation continued to remain unchanged, but pigs developed respiratory acidemia. Lung compliance and elastic respiratory work and power did not change significantly, yet VO_2 fell progressively during both cardiac output depression states (Table 2).

Table 1: Cardiac Function Variables (X ± SD)

		Cardiac Depression	
Variable	Normal	Moderate	Severe
O_2ex(%)	24 ± 8	38 ± 11*	51 ± 15*
CO(L/min)	5.2 ± 1.1	3.2 ± 0.6*	2.1 ± 0.5*
SV(ml)	40 ± 9	30 ± 5*	23 ± 5*
MAP(mmHg)	80 ± 14	74 ± 16	57 ± 16*
PAOP(mmHg)	8 ± 4*	14 ± 4	16 ± 3

*p < .0001 compared to other states.

Table 2: VO_2 and Lung Mechanics (X ± SD)

		Cardiac Depression	
Variable	Normal	Moderate	Severe
VO_2(ml/min)	310 ± 60	280 ± 80*	250 ± 50*
V_t(ml)	174 ± 40	167 ± 30	157 ± 32*
RR(breath/min)	47 ± 10	49 ± 13	45 ± 13
C_L(ml/cm$H_2$0)	59 ± 108	25 ± 14	32 ± 18
Wel(ml.cm$H_2$0)	300 ± 180	350 ± 180	270 ± 160
P_R(10^2·Wel/min)	150± 90	150 ± 70	170 ± 120

*p<.04 compared to other states.

DISCUSSION. Patients who experience severe heart failure may benefit from mechanical ventilation because it allows blood that would otherwise perfuse respiratory muscles to be shunted to other organs in a circumstance where the respiratory muscles demand a high proportion of the cardiac output. Increased elastic respiratory work may accentuate the cardiac output fraction sent to respiratory muscles. Despite heart failure severe enough to increase O_2 extraction to 50%, our pigs experienced no change in lung compliance or elastic work or power of breathing. Thus, poor lung mechanics probably do not contribute to the development of ventilatory failure in patients with acute heart failure.

During mechanical ventilation, animals with heart failure do not experience a drop in VO_2 until O_2 extraction exceeds 50%.[2] This fact implies that depressed cardiac function does not limit VO_2 until over 50% of available O_2 is extracted during mechanical ventilatory support.

However, our pigs experienced decreased VO_2 when only 38% of available 02 was extracted. They began to show metabolic limitation with only moderate heart failure. Thus, the degree of heart failure necessary to decrease VO_2 by limiting O_2 delivery occurs earlier and with a lesser degree of heart failure when animals breathe spontaneously compared to when they receive mechanical ventilation.

We conclude that spontaneous ventilation during acute heart failure is detrimental because it metabolically stresses the animal, limiting O_2 delivery, and causing VO_2 to fall. Further, lung compliance and elastic pulmonary work and power do not change during moderate or severe acute heart failure. Thus, metabolic rather than mechanical etiologies are probably responsible for the genesis of ventilatory failure during heart failure.

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Supported by AHA-GA N0002, BSRG 507RR05364

TITLE: **MYOCARDIAL BLOOD FLOW DURING CARDIAC SURGERY: VALIDATION OF THE Xe-133 METHOD IN DOGS**

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AFFILIATION: Departments of Anesthesia, Neurology, and Surgery, Wake Forest University Medical Center, Winston-Salem, North Carolina 27103

Introduction: Coronary artery bypass surgery is one of the most widely practiced procedures for the treatment of patients with coronary atherosclerosis, yet a simple and rapid method for assessing the effectiveness of the procedure while it is being performed is not currently available. We have developed a miniature, solid-state gamma ray detector small enough to suture directly to the myocardium to measure the uptake and clearance of minute amounts of Xe-133. Accurate estimates of regional myocardial blood flow (rMBF) are available within 5 minutes of the initial tracer delivery. We report here the validation of this method using microspheres in a canine model.

Methods: After IRB approval, 6 mongrel dogs (18-22kg) were studied. Each animal was anesthetized with 8 mg/kg thiopental IV, endotracheally intubated, paralyzed with pancuronium bromide (0.1 mg/kg), then maintained using 0.5% halothane in 70% nitrous oxide. PaCO2 was maintained at 35-40 mmHg. The right femoral and pulmonary arteries were cannulated for monitoring of mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP) and cardiac output. The left femoral artery was used for blood gas sampling. The left brachial artery was used as a reference organ for the microspheres (15 μm dia.). A polyproplyene catheter was placed in the left atrium for injection of both the Xe-133 and the microspheres. A branch of the left anterior descending coronary artery (LAD) proximal to the left ventricle was dissected free and a snare placed around it to provide a total occlusion model. Two pacing leads were placed near the root of the right atrial appendage for artificial pacing. Two cadmium telluride detectors (1 cm x 1 cm; approximately the size of 6 stacked dimes) were placed in teflon^R sheaths and sutured to the epicardium of the left ventricle, one in an area perfused by the LAD and the other proximal to the occlusion. MBF was measured by both Xe-133 desaturation and microsphere injection at 4 intervals: 1) baseline, 2) artificial pacing - heart rate increased to 190 bpm, 3) LAD occluded (unpaced), and 4) artificial pacing at 190 bpm after occlusion. The Xe-133 was injected after the microspheres except during interval 3 when the Xe-133 was injected just prior to occlusion and the microspheres just after. The studies were 20 minutes apart. Gentian violet was injected in the LAD at sacrifice to insure the reference detector was not overlying LAD territory.

Results: The results of these studies confirmed the good correlation between the Xe-133 measurements and the microsphere method. Regression analysis demonstrated a correlation of $r=0.56$ with a $p<0.001$ (Fig. 1). Fig. 2 shows the proportional change from baseline to each of the measurement intervals for the two measurement regions and for both methods. The relationship is excellent except for the total occlusion period where the Xe-133 method over-estimated flow. This phenomenon is well documented in the brain blood flow literature as the "look-through" problem, where the detector records counts from other areas when there is no Xenon delivered directly to the monitored area. The microsphere results were correlated with 3 MBF parameters, all which were significantly correlated but the height over area method, MBF_{15}, proved to be the most reliable.

Discussion: These experiments demonstrate the feasibility of obtaining accurate measurement of regional myocardial blood flow intraoperatively. The technique and apparatus are relatively non-obtrusive and do not extend the operation procedure appreciably. These data represent a global estimate of myocardial blood flow, but experiments are ongoing to assess the possibility of determining epicardial and endocardial compartmental flows. This method may lend itself to determining the adequacy of mammary artery graft capacity prior to chest closure. The method appears to be valid across a wide range of flow values but care must be taken when evaluating regions of total occlusion.

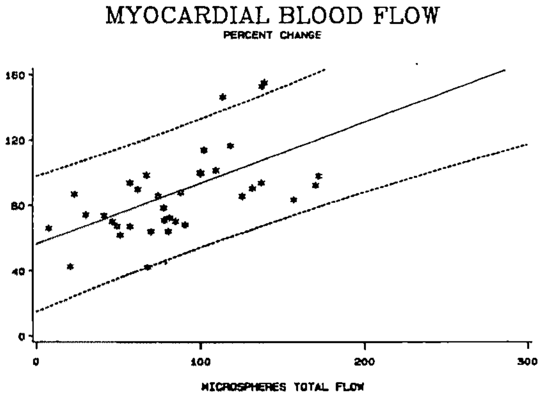

FIGURE 1.

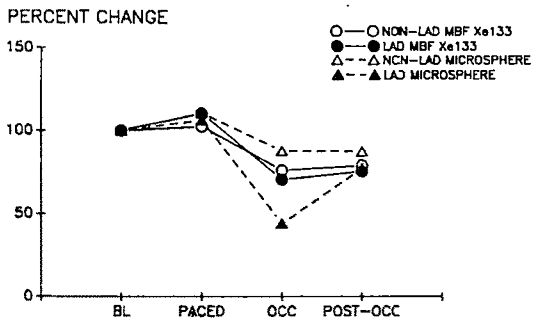

FIGURE 2.

TITLE: NEUROPSYCHOLOGICAL DYSFUNCTION FOLLOWING CARDIAC SURGERY: REPETITIVE TEST PERFORMANCE IN PATIENTS AND CONTROLS

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Introduction: Neuropsychological dysfunction following cardiopulmonary bypass (CPB) represents a major medical and economic problem, since at least 250,000 coronary artery bypass graft (CABG) procedures are performed each year. As the proportion of elderly patients under going bypass has increased, so has the incidence (5%) of postoperative stroke. A much higher percentage (>50%) of patients suffer ischemic neural injury of lesser magnitude as demonstrated by quantitative psychometric testing (1,2). The wide range of reported neuropsychological dysfunction (0-80%) is due in part to the type of tests used. One important source of variability between reports in the literature is test/retest reliability of the test instruments. We compared two groups of subjects to assess the effect of repetitive testing. We report here our experience with a short battery designed to assess manual dexterity, fatigability, attention, concentration, and visual motor coordination.

Methods: Following approval by our IRB, 30 patients undergoing hypothermic CPB gave informed, written consent to the study. Twenty-five normal volunteers served as controls, to assess test/retest realiability and the effects of practice and repetition on a subset of the battery. The patients were studied preoperatively and on the 5-7th postoperative day, while the controls were retested after 7 days. The outcome variable on these tests was time to completion. In order to minimize the effects of tester variability in timing and to acquire important additional information, the tests were timed by a computer. A Kurta graphics board was programmed so that the subjects' responses were timed and scored as well as being retrievable for later detailed analysis. In this manner, a performance curve across time can be generated to determine if fatigue or waning concentration plays a role in postoperative performance decrements. The test battery (table 1) was designed to be brief (50 min) and to discriminate between left and right hemisphere focal dysfunctions.

Results: Subjects were divided into 3 groups according to whether they 1) improved or remained unchanged, 2) declined 0-20% from the baseline tests, or 3) declined >20% from baseline. Table 2 shows the results from the 25 normal controls on 3 tests of motor function. The single subject who showed a change of greater than 20% fell from an outstanding level of performance to a superior level one week later. The normals usually performed within 10% of their previous level, with more than 90% showing a slight improvement in scores. In contrast, Table 1 shows that one-third of the patients showed a substantial decrease in performance following CPB. Twenty of 30 subjects showed at least a 20% decline from baseline in at least one test. Sixteen of 30 deteriorated at least 20% from baseline in at least two tests. This contrasts dramatically with the control subjects.

Discussion: The incidence of neuropsychological impairment in this sample confirms previous reports (1,2,3). These results indicate that postoperative higher cortical dysfunction is a common occurrence and relatively easy to document with a few, carefully chosen tests. This concise battery detects marked decrements in function in over half of the patients tested. It is important to note that on most of the tests half of the patients improved as did virtually all of controls. Normally, on tests of manual dexterity, a right-handed person performs at a level 10% better with the dominant hand than with the non-dominant. In our sample, 1 out of every 5 patients showed a postoperative performance where the dominant hand was demonstrably less dexterous than the non-dominant one. Reducing the level of right hand function to that of the left hand would be noteworthy handicap yet one that would escape the notice of a cursory neurologic exam or postoperative interview. The subjects in this study are being followed to define the time course of the their dysfunction and its impact upon their daily lives. Further studies are required to determine the etiology of these disorders.

Table 1: Neuropsychological Battery - CPB Patients

TEST	% > 0	% 0-20	% >20
Trail-making A	47	20	33
Trail-making B	74	0	26
Grooved Peg Board (D. Hand)	42	42	16
Grooved Peg Board (ND.Hand)	53	21	26
Finger Tapping (D. Hand)	64	17	29
Finger Tapping (ND.Hand)	68	8	24
Digit-Symbol/Symbol Digit	24	23	53
Visual Reaction Time Task	48	23	29

Table 2: Neuropsychological Battery - Controls

TEST	% > 0	% 0-20	% >20
Trail-making A	89	11	0
Trail-making B	96	0	4
Grooved Peg Board (D. Hand)	96	0	4
Grooved Peg Board (ND.Hand)	93	3.5	3.5
Finger Tapping (D. Hand)	93	7	0
Finger Tapping (ND.Hand)	93	7	0

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Title: THE DIFFERENTIAL COST OF ANESTHESIA AND RECOVERY WITH PROPOFOL-NITROUS OXIDE ANESTHESIA VERSUS THIOPENTAL-ISOFLURANE-NITROUS OXIDE

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Introduction A number of recent economic, political, and social changes have resulted in an increase in the number of surgical procedures performed on an outpatient basis. Over all, ambulatory surgical procedures now account for between 40-50% of all surgical procedures performed, and this percentage is still increasing. Since propofol has been shown in clinical studies[1,2] to be associated with more rapid recovery and a lower incidence of nausea and vomiting than standard anesthetic regimes, it is reasonable to assume that the use of propofol in the current practice of outpatient anesthesia may result in economic benefits to the institution and the patient.

The purpose of the study was to assess the recovery room profile of propofol in outpatient anesthesia, and to demonstrate its benefit over a standard technique involving thiopental for induction and isoflurane and nitrous oxide for maintenance. This was one of two centers participating in a comparative, randomized study evaluating the safety, efficacy and economic benefits associated with the use of propofol in outpatient anesthesia.

Methods The study was approved by the Institutional Human Investigation Committee. Ninety-nine ASA Class I-III patients consented to participate in the study. The patients were interviewed from one to a few days prior to surgery. The routine laboratory tests were performed at that time. The patient was monitored with EKG, blood pressure, pulse oximeter, CO_2 monitor and temperature. All patients had 1 mcg/kg of fentanyl prior to induction. The patients in the propofol group were induced with 2 - 2.5 mg/kg of propofol and maintained with 100 - 200 mcg/kg/min infusion of propofol with nitrous oxide-oxygen.

In the thiopental-isoflurane group, the patients were induced with 4 - 5 mg/kg of thiopental and then maintained with isoflurane and nitrous oxide.

Recovery from anesthesia was assessed by an evaluator who was unaware of the anesthetic technique used for each patient. Immediate recovery time, such as awakening, response to verbal command, and orientation was measured in both the operating room as well as in the recovery room.

Assessments were made to determine the time at which the patient was suitable to be transferred from Phase I to Phase II (step down area). Assessment for nausea and vomiting, ability to tolerate fluids, ability to sit independently and ambulate were made as appropriate. Suitability for discharge from the Phase II recovery area was also assessed for each patient. A brief postoperative followup questionnaire was completed which assessed the patients' subjective feelings regarding their abilities to eat, concentrate and resume normal activities.

Statistical methods: Frequency data was calculated by chi-square test. Other data was calculated by Student's t test. The latter presented as mean ± S.E.

Results The propofol group was older than the thiopental-isoflurane group, 49.12 ± 1.49 years vs. 43.32 ± 1.47 years ($P<0.01$), and had a longer operating time, 55.5 ± 1.83 min vs. 50.7 ± 1.20 min ($P<0.05$). The propofol group took a shorter time in Phase I recovery and total recovery time than the thiopental-isoflurane group, 41.68 ± 2.31 min vs. 56.08 ± 3.7 min ($P<0.01$) and 115.22 min ± 3.82 min vs. 134.42 min ± 5.13 min ($P<0.01$), respectively. In the thiopental-isoflurane group 15 of 50 patients (30%) had nausea and vomiting; however, in the propofol group only 4 of 49 patients (8.1%) had nausea and vomiting. The propofol group resumed normal activity (i.e., reading, watching TV) 7.93 ± 0.76 hours postanesthesia, whereas the thiopental-isoflurane group took 17.02 ± 1.21 hrs ($P<0.001$). Patients in the propofol group returned to work in an average of 1.5 ± 0.09 days compared to 2.0 ± 0.09 days for the thiopental-isoflurane group.

Discussion Patients in the propofol group averaged 15 min less time in Phase I than the patients in thiopental-isoflurane group. i.e., in 4,000 case/year facility, 1,000 nursing hours would be saved. In addition, patients in the propofol group had significantly lower incidence of nausea and vomiting than the thiopental-isoflurane group. Therefore, propofol group patients needed less nursing care and returned to more productive activity earlier than did the thiopental-isoflurane group.

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SONOGRAPHIC GUIDANCE OF CENTRAL VENOUS CATHETERIZATION

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Introduction:

Central venous catheterization has traditionally been performed using superfical anatomy to guide blind punctures. While this proceedure is generally effective, it can be time consuming and can result in injury to adjacent organs. With ultrasound more readily available in the operating suite, we examined the utility of sonographic guidance for central venous catheterization.

Methods:

Ninety patients undergoing the placement of superior vena cava catheters or pulmonary artery catheters were included in the study. This study met the requirements of our institutions Human Investigation Committee and written informed consent was obtained. A Codman OR 330 ultrasound unit with 5 and 7.5 mHz transducers was used in this study. The patients neck was prepared with antiseptic solution and draped as a sterile field. The ultrasound transducer, which is gas sterilized, is used to examine the patients neck. The internal jugular vein, carotid artery and apex of the lung were then localized. Holding the transducer directly over the internal jugular vein with one hand, an 16 ga. needle was advanced into the internal jugular vein. Ultrasound allowed visualization of the needle as it advanced into the jugular vein. Blood return was confirmed and a guidewire was advanced through the needle into the vein. Sonography confirmed that the wire was in the vein in each case. Dilators and catheters were then advanced over the guidewire in the standard method. In each case the time for the proceedure, the number of needle passes and complications were recorded.

Results:

The placement of the central venous catheter was successful in all 90 patients. The proceedure was performed in an average of 4min. 10 sec. The longest case required 6min. 30 sec. and the shortest was completed in 2min. 30 sec.. In 81 patients only a single needle pass was needed to enter the internal jugular vein. Two passes were required in 8 patients. In one patient with an unusually thick neck, 4 needle passes were required. In this series no arterial punctures, pneumothoraces or other complications occured.

Discussion:

With only a minimum of experience, the internal jugular vein can be identified using ultrasound. In addition to localizing the jugular vein, sonography allows the carotid artery and apex of the lung to be visualized and avoided. By using ultrasound the internal jugular vein could be punctured under direct guidance. Ultrasound allowed the operator to adjust the trajectory of the needle as it is advanced toward the vein. In addition the needle tip could be placed in the center to the vein to make passing the guidewire easier. Because of this direct guidance adjacent organs were not punctured and no complications occured in our series. Since ultrasound units are becoming increasingly available in surgical suites, they can be used to make the insertion of central venous catheters simpler and safer.

Title: FLUORIDE METABOLITES FOLLOWING PROLONGED EXPOSURE OF VOLUNTEERS TO DESFLURANE

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Introduction. Compared to isoflurane, animals anesthetized with the promising new volatile anesthetic desflurane [CF$_2$H-O-CFH-CF$_3$] (previously known as I-653) demonstrate a much smaller degree of metabolic breakdown.[1,2] Because the breakdown of volatile anesthetics to fluoride ion[3] and organic metabolites[4] may produce toxicity, we have extended these studies to volunteers given desflurane for prolonged periods.

Methods. This study was approved by our Committee on Human Research. Eight young healthy adult male volunteers were anesthetized with desflurane for 6.5 to 9 hrs (approximately 8 MAC-hrs). End-tidal desflurane concentrations were determined by infra-red analysis. Serum and/or urine samples were collected prior to anesthesia ("PRE"), at the end of exposure to desflurane ("END"), and at 4 and 24 hrs and 4 and 6 days after exposure. Fluoride ion levels were determined with a fluoride ion electrode, and nonvolatile organic fluoride in urine was assayed by sodium fusion.[1] Trifluoroacetic acid (TFA) was analyzed by a gas chromatographic-mass spectrometric procedure, with a limit of detection of 0.1 μM. Statistical comparisons were performed by a one-way analysis of variance.

Results: Serum fluoride ion levels after discontinuation of anesthetic administration did not differ from pre-anesthetic values (Fig. 1). Similarly, excretion of fluoride ion or organic fluoride (data not shown) in urine did not increase. However, peak serum TFA concentrations in the 3 volunteers for whom data are presently available were approximately 0.3 μM and peak urine TFA concentrations (found 24 hrs after desflurane anesthesia) were approximately 2 μM (Fig. 2). TFA levels prior to desflurane exposure were < 0.1 μM.

Discussion. Our results are consistent with those previously obtained in rats and swine and indicate that desflurane resists metabolic breakdown in humans more than any presently used inhaled anesthetics. The results from studies in animals imply that this relationship would not be modified by enzyme induction (our volunteers were not taking medications). However, the finding that TFA levels slightly increase above background levels after exposure of volunteers to desflurane demonstrates that a small degree of metabolism does occur. This finding also suggests that metabolism of desflurane results from oxidation of the alpha-hydrogen on the ethyl moiety.

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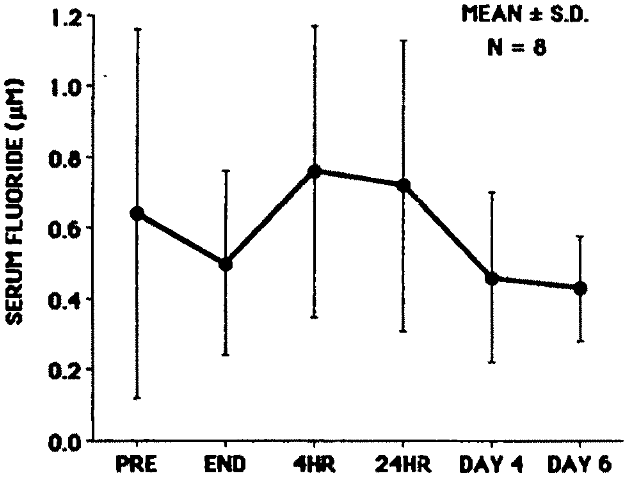

Figure 1. Serum fluoride ion concentrations before (PRE) and at various times after the administration of desflurane.

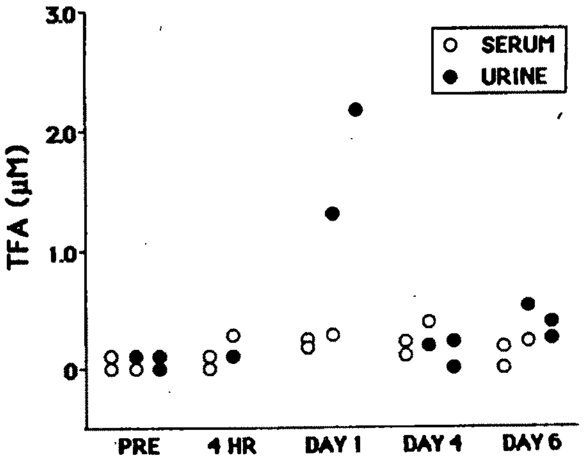

Figure 2. Serum and urine trifluoroacetic acid (TFA) concentrations before (PRE) and at various times after administration of desflurane.

Title: MUSIC IS USEFUL AS ADJUNCTIVE THERAPY POSTOPERATIVELY

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Introduction. In the immediate postoperative period pain, nausea, vomiting and anxiety are mixed with remaining effects from anesthesia and surgery. Music has been shown to be effective in reducing anxiety and the perception of pain in dentistry. This study evaluated the pain relieving properties of music therapy and its impact on the patients' memory of their immediate postoperative experience.

Methods. After approval by the institutional human investigation committee, 60 men and women, scheduled for thyroidectomy, parathyroidectomy or mastectomy gave their written informed consent to participate in the study. Patients who were ASA 1-3 and intact hearing were included. They were premedicated with Valium 5-10 mg PO. Anesthesia was induced with Pentothal 4-5 mg/kg and Fentanyl 2μg/kg and relaxed with succinylcholine or vecuronium, and maintained with O_2 + N_2O and isoflurane. The patients were randomized into three groups: Group 1 - no headphones and no music, group 2 - headphones but no music, and group 3 - headphones and music. Patients had preoperatively chosen music from instrumental works. Two classical tapes were offered, one with calming and the other of stimulative quality. One popular music tape of calming quality was offered. Within 15 min after arrival in the Post Anesthesia Care Unit (PACU), the headphones were placed on patients in Group 2 and 3 and music was delivered to the latter group.

Pain was evaluated with visual analogue pain scale (VAS) (0-no pain, 10-worst pain) every 15 min, as were hemodynamics and respiratory rate. Patients were given morphine 0.025 mg/kg i.v. every 5 min PRN in the PACU. Time in PACU was recorded as well as time until initial analgesic given on floor. Twenty-four hours postoperatively and again one month later, patients were asked to complete a questionnaire about their PACU experience. Differences among the three groups were evaluated with analysis of variance with repeated measure.

Results. Demographic data (Mean ± SEM) and surgery is shown in table. No differences were found among the three groups in these variables.

	Group 1	Group 2	Group 3
n	20	20	20
Women/men	19/1	19/1	18/2
Age, years	52±3	54±4	46±3
Weight, kg	70±4	76±5	74±3
Mastectomy	11	10	9
Thyroidectomy	4	6	8
Parathyroidectomy	5	4	3

There was no difference among the three groups in pain score, morphine requirement, hemodynamics or time in PACU. Pain score was initially 6 (range 4-8) and decreased over 90 min to 5 (range 3-7). Patients in all three groups were given a mean of 1.5 doses of morphine during the first two 30 min periods and 0.75 doses during the last 30 min in PACU. All patients had stable hemodynamics and respiration. The stay in PACU was 90 min (range 60-150). Pain relief was not required on the floor in the music group until more than 6.5 hours after discharge from PACU, significantly longer than group 1 and 2 where pain relief was needed after 3.75 and 4.75 hours ($p<0.05$).

The memory of PACU was significantly more pleasant in group 3 compared to the other two groups both one day and one month postoperatively.

Discussion. The pain relieving properties of music experienced in dentistry could not be reproduced in the immediate postoperative period in this study. It could be speculated that music is effective only in low grade pain, which would explain the decreased need for pain medication later in the postoperative period seen in the music group. The mechanism could be a relaxing effect of music enabling the patient to tolerate low grade pain. Most important, music had a pronounced salutary effect on patients' memories of the PACU period as pleasant, with or without pain, nausea, vomiting and anxiety.

Conclusion. Music
- did not decrease the perception of pain in PACU
- did not decrease the need for morphine in PACU
- did not decrease PACU time
- did increase time until initial analgesic needed on floor
- made the memory of PACU more pleasant

Title: PLACEMENT OF INTERPLEURAL CATHETERS IN PIGS - IS NEEDLE SIZE AND TECHNIQUE IMPORTANT?

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Introduction. Interpleural (IP) placement of catheters for injection of local anesthetics is a relatively new technique for postoperative pain relief after thoracic and upper abdominal procedures. Its pain relieving effect is well documented but there is still lacking documentation of technical complications. This study reports pulmonary complications after placement of 68 IP catheters. Sharp and dull needles are compared. Identification of the space with piston being drawn in by negative pressure (PINP) or loss of resistance (LOR) was evaluated as well as two size syringes for PINP procedure.

Methods. Following animal review board approval 38 swine, 36-44 kg, were anesthetized with ketamine and fentanyl, and relaxed with succinylcholine. They were placed supine and ventilated to ensure normal arterial blood gases. IP catheters were placed in the fifth to seventh intercostal space about 20 cm from anterior midline while disconnected from ventilator. A well-moistened 5 (Syr-5) or 20 (Syr-20) ml glass syringe containing 3-10 ml air was attached to an epidural needle. We used either a sharp 18-gauge Hustead or a dull 14-gauge Tuohy epidural needle. The pleural space was identified by the piston being drawn inward by the negative intrathoracic pressure (PINP) or by intermittent LOR. The side used for different needles and syringes varied randomly. The catheter was advanced 10-15 cm into the pleural space, the needle removed and ventilation resumed. They were monitored with an ECG, fiberoptic arterial and pulmonary artery catheters. Fick cardiac output and shunt were calculated and breath sounds and peak inspiratory pressure (PIP) were recorded. After one to four hours the chest was opened, via a sternotomy, and presence of pneumothorax and/or other lung damage was noted as well as catheter position and lung pathology. Chi-square analysis was used for comparison of different needles, syringes and techniques.

Results. Sixty-eight catheters were placed (Table), 64 were located IP and four in lung tissue (Cath.Lung). On 27 occasions the piston was not drawn in and LOR indicated the IP position. When the chest was opened a small lung hematoma (diameter $\leq$ 5mm) was seen close to the place of needle insertion and a larger hematoma (diam. 6-20 mm) on 11 and 15 occasions respectively. A hole in lung tissue was found nine times and a pneumothorax in 31. The pneumothorax was of significant size (L Pnx) with tension at only three occasions. Sharp needles caused more catheters to be placed in lung tissue but had fewer pneumothoraces than dull needles (Table). The larger 20 ml syringe was more advantageous than the 5 ml syringe regarding a higher success rate with PINP technique ($p<0.001$) and associated with less lung damage ($p<0.05$)(Table). The PINP technique was associated with fewer sticks in lung tissue ($p<0.05$).

	All	Sharp	Dull	Syr-5	Syr-20	PINP	LOR
n	68	34	34	34	34	41	27
PINP	41	23	18	11	30	X	X
LOR	27	11	16	23	4	X	X
Cath.IP	64	30	34	31	33	40	24
Cath.Lung	4	4	0	3	1	1	3
Hemat.$\leq$ 5	11	6	5	7	4	8	3
Hemat.> 5	15	6	9	9	6	6	9
Hole lung	9	6	3	7	2	2	7
L Pnx	3	1	2	2	1	1	2
S Pnx	28	5	23	10	18	17	11
Tens Pnx	3	1	2	2	1	1	2

Discussion. These results confirm an earlier report (1) that lung trauma is not uncommon with this technique. The frequency of serious complications is much lower in the present study, partly due to a lower rate of lung pathology. Small pneumothoraces seen mostly with 14 gauge dull needles was only seen twice together with a hole in the lung tissue but without air leak. Most small pneumothoraces were probably due to air leak through needle at disconnection from syringe. Large pneumothoraces were all associated with lung lesion and an air leak. The initial sign was an increased pulmonary shunt followed by increased PIP and in one case hypotension and tachycardia. Sharp needles had a higher rate of intrapulmonary catheter placements but lower rate of tension pneumothoraces compared to dull needles, all nonsignificant differences. Comparing PINP and LOR in this study is not appropriate since in those cases where PINP worked LOR was not tried. A combined technique seems optimal from our results. The IP space was found earliest with LOR technique in some cases with both sharp and dull needles, but in few cases with the larger syringe. The use of a 20 ml syringe resulted in a high success rate with PINP technique and significantly less lung trauma.

Conclusions.

- Interpleural catheter placement is frequently associated with harmless side effects such as small hematoma, nonleaking lung pucture or small pneumothoraces.
- The risk for serious complications such as tension pneumothorax is low but exists irrespective of technique, needle or syringe used
- A technique where IP space identified with a combined PINP and LOR technique using a large syringe with either needle gives optimal placement results with a low rate of complications.

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Title: EFFECTS OF VERAPAMIL ON SYNAPTIC TRANSMISSION AND AXONAL CONDUCTION

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Introduction: The arrival of a nerve impulse at a synaptic knob increases the membrane premeability to Ca^{2+} and the resultant Ca^{2+} influx into the presynaptic nerve ending causes release of acetylcholine from the nerve ending into the synaptic cleft, resulting in synaptic transmission (1). Calcium channel blockers prevent Ca^{2+} influx into the cell (2), and thus may interfere with the release of acetylcholine and synaptic transmission. To test this possibility, the present study was undertaken to verify the effects of verapamil, a calcium channel blocker, on synaptic transmission in the superior cervical ganglion (SCG) of the rat.

Methods: The study was approved by the institutional animal investigation committee. The SCG of six Dial urethane-anesthetized rats were removed along with the pre- and postganglionic nerve trunks, and placed in a tissue bath superfused with Kreb's Ringer's solution and gassed with 95% O_2 and 5% CO_2 at 35-37C. The ganglion was fixed in the bath by means of pins, while the pre- and postganglionic nerve trunks were pulled in separate suction electrodes for stimulation and recording purposes respectively. Verapamil, in doses of 0.0625 mg, 0.125 mg, 0.25 mg and 0.5 mg, in a volume of 0.2 ml, was added to the tissue bath in close proximity of the ganglion. The compound action potential (CAP) of the postganglionic nerve trunk in response to stimulation of the preganglionic nerve trunk was recorded before and after verapamil delivery, and the percent suppression of its amplitude was used as a measure of response to verapamil. Normal saline served as control. In a separate set of experiments, the effects of similar doses of verapamil on axonal conduction were studied on isolated cervical sympathetic trunks and vagus nerves. Recovery time from the effects of verapamil was measured. The nonparametric Friedman test and Student t-test were used to analyze data. $P<0.05$ was considered statistically significant.

Results: Verapamil caused depression of the synaptic transmission in a reversible dose-dependent manner ($P<0.01$). The decrease in the amplitude of the CAP was 10, 30, 50, and 90 % for the various doses of verapamil (0.0625 mg, 0.125 mg, 0.25 mg and 0.5 mg) respectively. It took 8 minutes for the CAP to recover when 0.0625 mg verapamil was applied, and 90 minutes when 0.5 mg was applied ($P<0.01$). Qualitatively, verapamil had similar effects on the cervical sympathetic trunk and vagus nerve. Quantitatively, the depression was 15-20% less at the various doses, and recovery time about one third shorter ($P<0.05$).

Discussion: The results indicate that synaptic transmission is more sensitive to the inhibitory action of verapamil than axonal conduction is. The inhibitory action of verapamil on synaptic transmission in the superior cervical ganglion could be attributed to its calcium channel blocking property, i.e., by blocking Ca^{2+} entry into the preganglionic nerve endings, resulting in failure of acetylcholine release at the synapse and depression or cessation of synaptic transmission. However, since verapamil also blocks axonal conduction in the sympathetic trunk and vagus nerve, its mechanism of action on synaptic transmission and axonal conduction may be secondary to sodium channel blocking property; a mechanism similar to that of local anesthetics. The fact that synaptic transmission is more sensitive to the inhibitory effects of verapamil than axonal conduction is suggests that calcium channel blocking properties of verapamil may have a contributory role in depressing synaptic transmission. The results also raise the question whether verapamil may have the potential to be used as an anesthetic for local and regional anesthesia.

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Title: INCREASE IN EXTRAVASCULAR LUNG WATER AND DECREASE IN LUNG LYMPH FLOW RESULTING FROM POSITIVE END EXPIRATORY PRESSURE (PEEP) AFTER INHALATION INJURY IN SHEEP

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Introduction. PEEP is commonly used to increase oxygenation in patients with acute lung injury. In healthy animals PEEP results in reversible increase in extravascular lung water (EVLW) and a reversible decrease in lung lymph flow (LQ) (1). In the present study we evaluated the effect of PEEP on EVLW and LQ in animals with increased pulmonary microvascular permeability secondary to inhalation injury; A model which simulates ARDS.

Methods. Six sheep with arterial, left atrial, lung water and Swan-Ganz catheters were used. The lung lymphatic was cannulated and animals were given one week to recover. Tracheostomy was performed and the animals subjected to smoke inhalation injury by insufflating the lungs with 48 breaths of cotton smoke under halothane anesthesia (2). Animals were mechanically ventilated (tidal volume 15 cc/kg, FiO_2 adjusted to prevent hypoxia and respiratory rate to maintain pCO_2 below 30 mmHg) and studied 24 hours later in awake state. The protocol consisted of three one hour periods. First the animals were ventilated with no PEEP (Period I), then with 10 cm H_2O PEEP (Period II) and finally with no PEEP again (Period III). EVLW and cardiac output (CO) were measured at the end of each study period by the double indicator dilution method. Systemic arterial pressure (MAP), pulmonary artery pressure (PAP), left atrial pressure (LAP), pulmonary artery occlusion pressure (PAOP), heart rate (HR), LQ and arterial blood gases were recorded every 15 minutes. The data were analyzed using an analysis of variance and Duncan's multiple range test. This study was approved by the institutional Animal Care and Utilization Committee.

Results. Increase in PEEP resulted in a significant increase in EVLW which returned toward baseline when PEEP was removed. LQ decreased significantly with application of PEEP and increased above baseline when PEEP was removed. When PEEP was increased to 10 cm H_2O, CO decreased by 17% (Figure 1). As PEEP was increased to 10 cm H_2O, PAP increased on the average by 4 mmHg, LAP by 4 mmHg and PAOP by 3 mmHg (Figure 2). All of the above changes were statistically significant. There were no significant changes in MAP or HR.

Discussion. In our smoke inhalation injury animal model with pulmonary edema, PEEP resulted in a reversible increase in EVLW and a reversible decrease in LQ. We propose that PEEP retards LQ partly by mechanical obstruction of intrathoracic lymphatics which results in pulmonary interstitial fluid accumulation, measured as increased EVLW. We suggest that as PEEP is removed, the pooled lymph drains from the lungs, indicated by the higher than baseline LQ during Period III. Other causes, such as PEEP allowing for distribution of thermal indicator through a larger fraction of lung water (3) cannot be ruled out since the increase in EVLW was greater than the total decrease in LQ. PEEP should be used cautiously in view of the possible increase in EVLW and decrease in pulmonary bacterial clearance secondary to decreased pulmonary lymph flow.

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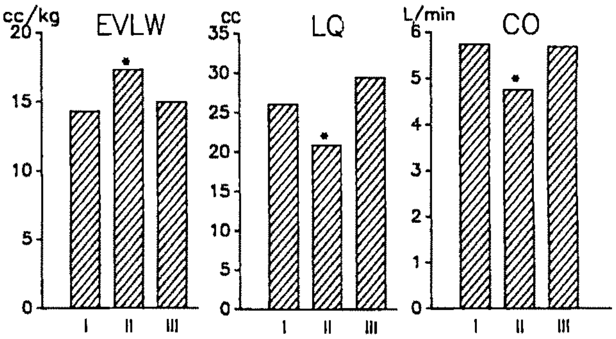

Figure 1

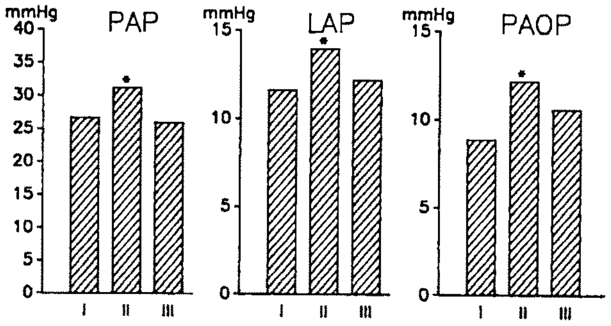

Figure 2

COMPARISON OF ENOXIMONE WITH DOPAMINE FOLLOWING MITRAL VALVE SURGERY.

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INTRODUCTION.

Mitral valve surgery is frequently complicated by a post-operative low cardiac output state which requires inotropic support either alone or in combination with vasodilator agents.

Enoximone is a new phosphodiesterase inhibitor with both inotropic and vasodilator properties.

This investigation examines the efficacy of enoximone, in facilitating weaning from cardiopulmonary bypass (CPB) in comparison to dopamine, in a group of patients who had undergone mitral valve surgery as a single or combined procedure and in whom initial weaning from CPB was unsuccessful.

METHODS.

Following hospital ethical committee approval and informed patient consent, 17 patients undergoing mitral valve surgery, either alone (10 patients) or combined with aortic valve replacement or coronary artery bypass grafting (7 patients) were investigated after failure to wean from CPB at the first attempt.A total of 10 patients received enoximone (E) and 7 patients dopamine (D). Unsuccessful weaning was defined as cardiac index (CI) <2.0 lmin^{-1}m^{-2} or systolic arterial pressure < 80 mmHg and pulmonary capillary wedge pressure (PCWP) > 20mmHg.In these patients full CPB was reinstituted and patients randomised to receive either E(1mgkg^{-1} followed by an infusion of 10µgkg^{-1}min^{-1}) or D(continuous infusion at 7µgkg^{-1}min^{-1}).Five minutes after commencing either infusion a further attempt at weaning was made and serial measurements of the systemic and pulmonary artery pressures, PCWP, central venous pressure (CVP) and cardiac output, using a thermodilution method were performed. From these measured haemodynamic parameters we derived values for mean arterial pressure (MAP), CI, systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Measurements were performed prior to CPB (Control) and 5, 10, 15, 30, 45, 60, 90, 120, 180 and 240 minutes after successful weaning from CPB.

Statistical analysis performed, was analysis of variance for repeated measurements to compare within group data during the study period (ANOVA Statview 512+) and unpaired t-tests for inter-group analysis at each time period. Significance was assumed if $p < 0.05$.Mean values (±SD) are shown.

RESULTS.

There were no significant differences between the two groups of patients with respect to age, bypass time or aortic cross-clamp time. All patients were successfully weaned from CPB at the second attempt with inotropic support as described.

HEART RATE: Mean values were higher for D at all times following CPB when compared to E which was statistically significant at 30 and 45 minutes.Mean values of heart rate for E, showed little change from a control value of 83 beats.min^{-1} (±11) with a range of means -2% to +6.3% of this. For D there was an increase of +2.4% to +23.8% from the control 84 beats.min^{-1} (±24) significant at 10,30,45 and 60 minutes.

MAP: Mean values were lower for E at all times compared to D and a significant difference found at 15, 30 and 45 minutes. There was a significant reduction in MAP for E until 90 minutes, from a control mean 79 mmHg (±11.9) with the mean values for all the measurement times ranging -3.2% to -21.1% of this value. D demonstrated a range of means -7.1% to +13.4% from a control mean of 76 mmHg (±15.2) with the highest value at 180 minutes achieving statistical significance compared to the control value.

CI: Comparing E against D, mean values were always higher for E and statistically significant at 10, 30, 45 and 60 minutes. For E CI rose from a control value of 1.9 lmin^{-1}m^{-2} (±0.5) with means +27.4% to +50.8% of this value, a significant increase at all times. CI also increased for D at all times from 1.7 l.min^{-1}.m^{2}. (±0.5) by +13.2% to +35.3% during the post CPB period, values which were found to be statistically higher at 30.180 and 240 minutes.

PVR: There was no difference between the mean values for E and D at any time measured. However there was a fall from a control value for E of 329 dynes.s.cm^{5}.m^{-2}. (±97) with a range of mean values -18.9% to -42.2%, which at all times represented a significantly lower value than the control.D showed little change in PVR during the study period with a control of 252 dynes.s.cm^{5}.m^{-2}. (±84) with mean values +4.2% to -24.4% of this, not achieving significance at any time.

SVR: There was a highly significant lower SVR at all studied times following CPB for E when compared to D.Within group analysis demonstrated a range of mean values -34.8 % to -48.3% of the control 1620 dynes.s.cm^{5}.m^{-2}. (±419), values which were always significantly lower.There was no significant change for D when compared to the control mean 1832 dynes.s.cm^{5}.m^{-2}. with values -12.1% to -26% of this.

DISCUSSION.

This preliminary study has demonstrated that enoximone is as effective as dopamine in weaning patients from CPB following mitral valve surgery. It produces a significant increase in cardiac output with the benefits of a marked reduction in SVR and with no noticeable effect on heart rate.Further investigation with larger numbers of patients and with other agents appears warranted to establish the role of enoximone in post-operative low output states.

Title: **EFFECT OF ANESTHETIC TECHNIQUE ON THE POSTOPERATIVE PCA MORPHINE REQUIREMENT: SQ-PCA VS IV-PCA**

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Introduction: Patient-controlled analgesia (PCA) is an established method for administering opioid analgesics in the postoperative period (1). However, the effect of intra-operative opioid administration on the postoperative analgesic requirement has not been previously investigated. We designed a study to evaluate the intravenous (IV) or subcutaneous (SQ) PCA morphine requirement after intra-abdominal surgery with either an inhalational or opioid-based anesthetic technique.

Methods: Fifty-three consenting ASA I-II adult patients undergoing intra-abdominal operations (e.g. cholecystectomy, colectomy) were randomly assigned to one of two treatment groups according to an IRB-approved protocol. All patients received premedication with diazepam 10 mg po. Anesthesia was induced with fentanyl 1.5 ug.kg^{-1}, thiopental 4 mg.kg^{-1} and vecuronium 0.1 mg.kg^{-1} iv. Maintenance of general anesthesia consisted of either isoflurane 0.5-2% and nitrous oxide 67% in oxygen, or sufentanil infusion 0.25-1.0 ug.min^{-1} (mean dose equalled 115±56 ug) and nitrous oxide 67% in oxygen. In the recovery room, patients were administered incremental doses of morphine sulfate, 1-2 mg iv, as needed to control acute pain prior to initiating PCA therapy with a Baxter PCA Infusor™. This disposable, non-electronic PCA device was connected to either the patient's existing IV catheter (IV-PCA) or to a 23 ga. butterfly catheter placed SQ in the forearm (SQ-PCA). The IV-PCA group received morphine 2 mg (0.5 ml) bolus injections, while the SQ-PCA group received 3 mg (0.5 ml) bolus injections. The postoperative morphine usage and pain analog scores (0 = no pain to 100 = severe pain) were evaluated at 8h intervals. At the end of PCA therapy, patients completed a questionnaire assessing the effectiveness of their postoperative pain management. Data are presented as mean values (±S.D.) and were analyzed using ANOVA and Chi-square tests, with $p<0.05$ considered significant.

Results: The two anesthetic and two PCA treatment groups were comparable with respect to average age (50-57 yr), weight (71-78 kg) and duration of surgery (172-185 min), as well as sex distribution (2M:1F). The isoflurane anesthetic group required significantly more morphine in the recovery room (17±7 mg vs 7±6 mg in the sufentanil group, $p<0.001$). However, the total PCA morphine requirement (mg per 40h) did not differ between the two anesthetic group irrespective of whether it was administered by IV-PCA (isoflurane: 75±34 mg vs sufentanil: 85±36 mg) or SQ-PCA (isoflurane: 76±57 mg vs sufentanil: 94±41 mg). The onset of analgesia was slower with SQ-PCA (8.2±4.5 min vs 5.2±3.2 min with IV-PCA). Although the SQ-PCA group required slightly more morphine than the IV-PCA group (Fig. 1), there was no difference in postoperative pain scores or patient satisfaction with their PCA therapy (Table 1). Finally, side effects were comparable in the two PCA treatment groups.

Discussion: Compared to a standard inhalational anesthetic technique, the use of a narcotic-based technique significantly decreased the analgesic requirement in the recovery room. However, the anesthetic technique had no effect on the requirement for parenteral analgesic medication after discharge from the recovery room. As suggested in a recent report (2), SQ-PCA can provide acceptable postoperative analgesia. SQ-PCA and IV-PCA were equally effective in controlling pain after intra-abdominal surgery and almost all patients indicated that they would request PCA therapy in the future. In fact, 56% of the patients indicated that they felt the benefits of PCA would justify an additional hospital charge for its use. In conclusion, this study demonstrates that the anesthetic technique has no apparent effect in the PCA analgesic requirement and that SQ-PCA is a viable alternative to IV-PCA for managing postoperative pain after major surgical procedures.

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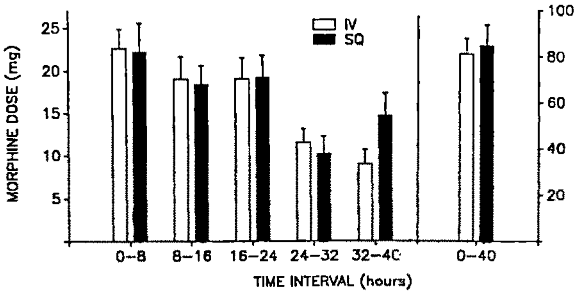
Table 1: Effectiveness of PCA therapy and side effects (% in each treatment group)

	IV-PCA	SQ-PCA
Minimal discomfort	69	74
Adequate analgesia	92	100
PCA preference	100	93
Drowsiness	46	48
Nausea	19	7
Itching	19	26

Figure 1:



Title: AMRINONE VERSUS DOPAMINE FOLLOWING CARDIAC SURGERY IN CHILDREN.

Authours: R.H. Taylor, FFARCS, P.W. Skippen, FFARACS, D Bohn, FRCPC.
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INTRODUCTION: Amrinone is a non-glycosidic, non-adrenergic inotropic agent with vasodilator properties. The use of this drug has been studied in adult patients(1), but reports of its effects in children are limited.(2) The aim of the current study was to determine if amrinone offers any advantages over dopamine in children following cardiac surgery.

METHODS: After institutional approval, and informed, parental, written consent children were randomly assigned to receive either dopamine or amrinone as clinically indicated for positive inotropic effect.

Entry criteria into the study were as determined by the clinical judgement of the ICU physicians. The right (RAP) or left (LAP) atrial pressures were maintained at greater than 12 mmHg throughout the study by the use of volume expanding fluid (colloid).

A baseline hemodynamic study was performed using the indocyanine-green dye dilution technique in duplicate.

Dopamine was commenced at 5mcg/kg/min and increased at 5 mcg intervals to a maximum dose of 20 mcg/kg/min at 30 minute intervals.

Amrinone was given as a bolus of 1 mg/kg followed by dose increments similar to the dopamine group. Further hemodynamic studies were performed at the end of each dose schedule.

After completion of the study the requirement for inotrope was reassessed in each patient and adjustments made accordingly.

Unpaired t-test was used for between group analysis and paired t-test for within group analysis. Chi-squared test was used for non-parametric data. Differences were considered significant for $p < 0.05$.

RESULTS: Of 13 children studied, 5 received dopamine (DOP) and 8 received amrinone treatment (AMR).

The ages, weights, duration of cardiopulmonary bypass and aortic cross-clamp were similar for the two groups, as were all baseline hemodynamic data.

There was a dose related increase in the heart rate (HR) of children in the DOP group. In one patient in this group the study had to be discontinued due to the development of a rapid sinus tachycardia prior to the last dose increment.

HR increased in the AMR group at the first two dosage increments, but at higher doses there was no difference from baseline.(Table 1.)

Mean arterial (MAP), pulmonary arterial (PAP), left atrial (LAP) and right atrial (RAP)/ central venous (CVP) pressures were not different between the two treatment groups and did not change within either group with dose.

The cardiac index showed a significant dose related increase in both groups.(Table 2.)

The stroke volume index (SVI) did not change with dosage in the DOP group, but increased in a dose related manner in the AMR group of children. (Table 3.)

Systemic and pulmonary vascular resistance were unchanged in both groups.

No child needed to return to the operating-room due to bleeding or other complication and there were no deaths during the period of study.

DISCUSSION: Dopamine and amrinone are both effective at increasing cardiac index in children following cardiac surgery.

Dopamine appears to have a marked positive chronotropic effect, in the manner in which it was administered to these children.

This was primarily a clinical study and in most children a vasodilator agent was used, eg phenoxybenzamine given during surgery or nitroglycerine infusion concurrently. Thus, the reported systemic vascular resistance probably does not reflect the sole inotropic effect. The increase in SVI and lack of tachycardia at higher doses with amrinone indicate that it may be effective as a positive inotrope, as reported by others in adult patients(1).

Further studies are required to determine if there are advantages to the use of amrinone over dopamine in children.

ACKNOWLEDGEMENTS: The authours would like to thank Winthrop Laboratories for their support with this study.

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Table 1

Dose (mcg/kg/min)	0	5	10	15	20
HR DOP	106.2	116.0	131.8*	148.4*	150.8*
	±9.52	±4.69	±3.97	±3.63	±8.38
HR AMR	125.1	137.3*	132.3*	128.4	128.1
	±8.05	±7.54	±5.88	±5.58	±4.47

Data are mean values ±SEM *$p < 0.05$

Table 2

CI DOP	3.77	4.15**	4.49	4.82**	5.23*
	±0.38	±0.39	±0.56	±0.43	±0.47
CI AMR	2.94	3.31	3.48*	3.64**	3.78*
	±0.28	±0.34	±0.34	±0.38	±0.43

Data are mean values ±SEM *$p < 0.05$ **$p < 0.01$

Table 3

SVI DOP	36.6	35.6	33.2	31.8	34.0
	±6.19	±3.68	±3.71	±2.03	±2.12
SVI AMR	22.8	23.6	25.9*	27.9**	29.1*
	±1.81	±2.12	±2.57	±2.70	±3.46

Data are mean values ±SEM *$p < 0.05$ **$p < 0.01$

Title: **ETOMIDATE-INDUCED EEG BURST SUPPRESSION MAINTAINS HEMODYNAMIC STABILITY DURING INDUCTION AND TRACHEAL INTUBATION**

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Introduction: Although many drugs have been used to attenuate the cardiovascular response to endotracheal intubation, the dosages recommended are a population estimate and cannot predict individual dosage requirements. A minimal time lag between drug levels and EEG effects has been shown for etomidate (1), an anesthetic associated with minimal alterations in hemodynamic variables (2). The present study was designed to determine if etomidate-induced EEG burst suppression (a stage of deep anesthesia) will maintain hemodynamic stability during induction and endotracheal intubation in neurovascular patients, many of whom also have coronary artery disease.

Materials and Methods: Following approval of our institutional review board (IRB), 12 consenting patients undergoing carotid endarterectomy or intracranial aneurysm surgery were studied. A radial arterial line, electrocardiogram (ECG) and 2 channel computerized EEG (Interspec^R-Neurotrac^R) were placed in each patient for the continuous recording of mean arterial blood pressure (MAP), heart rate (HR) and raw EEG in each cerebral hemisphere. EEG power values (in picowatts-pW) from the 2 raw EEG channels were averaged for each 2 sec epoch for a total of 15 epochs. Prior to induction of anesthesia, baseline (awake) measurements of MAP, HR, and EEG power were obtained. Immediately after bolus doses of etomidate 0.2 mg/kg iv and vecuronium 0.2 mg/kg iv, a continuous iv etomidate infusion was administered at a rate of 20 mg/min. When an isoelectric raw EEG (recorded at a gain of 30-40 microvolts) separated by 1-2 sec bursts of activity was attained, the etomidate infusion was stopped. At this time endotracheal intubation was performed. The values for HR, MAP, and EEG power were recorded at burst suppression, and at 30 and 90 sec post-intubation. These values were compared to their baseline (awake) measurements using two-tailed paired t-tests and a $P<0.05$ was considered significant.

Results: Figure 1 summarizes the hemodynamic and EEG findings. When compared to their awake values, no significant changes in HR or MAP were found at burst suppression, and at 30 and 90 sec post-intubation. Duration of laryngoscopy was 21±6 sec. Burst suppression was reached in 211±28 sec and was associated with a highly significant decrease in EEG power which was maintained at 30 and 90 sec following intubation. The average dose (bolus plus infusion) of etomidate used was 1.05±0.3 mg/kg.

Discussion: Autoregulation of cerebral blood flow may be lost or impaired in patients with cerebrovascular disease. Consequently, significant swings in MAP can produce dangerous increases or decreases in cerebral blood flow and volume. Although thiopental has favorable "brain protective" properties, the dosage required can depress MAP sufficiently to jeopardize both cerebral and myocardial perfusion, especially in the elderly or critically ill neurovascular patient, many of whom also have coronary artery disease. Conversely, light levels of anesthesia in these patients can lead to dangerous levels of hypertension and tachycardia. Etomidate-induced EEG burst suppression probably offers "cerebral protective" effects that are similar to thiopental (2) with less risk of significant decreases in myocardial and cerebral blood flow. Furthermore, this etomidate-based EEG model appears to ensure a depth of anesthesia which is sufficient to prevent hypertension and tachycardia at endotracheal intubation.

References:

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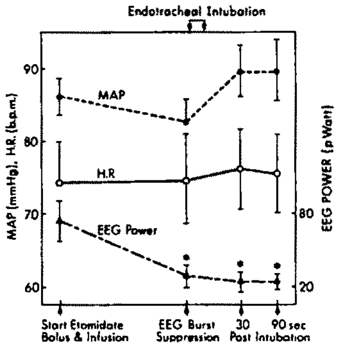
Figure 1: **Hemodynamic values during etomidate induction and intubation at burst suppression on EEG**



Values are expressed as mean ± S.E.

*** p<0.01 vs baseline awake values**

TITLE: **AN EVALUATION OF PH-ADJUSTMENT OF MEPIVICAINE FOR INTERSCALENE BRACHIAL PLEXUS ANESTHESIA.**

AUTHORS: J.E. Tetzlaff, M.D., H.J. Yoon, M.D., J.F. O'Hara, Jr., M.D., J.A. Reaney, M.D., D.I. Stein, M.D.

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Introduction: Addition of bicarbonate to local anesthetics has been shown to and increase the speed of onset of block[1-3] and increase duration.[3] Adjustment of pH to favor non-ionized form, which facilitates penetration of the nerve cell membrane, is the postulated mechanism.

This study was designed to evaluate the time of onset of surgical anesthesia and duration of interscalene block of the brachial plexus for shoulder surgery.

Methods: This study was approved by the Institutional Review Board.

Forty patients for shoulder surgery were selected. Written informed consent was obtained. Patients were randomized into a control and study group. Control group received an interscalene block with 40 ml of 1.4% mepivicaine with 1:200,000 epinephrine. Study group received interscalene block with 40 ml of 1.4% mepivicaine, 1:200,000 epinephrine with 4 ml of bicarbonate (1 meq/ml). Block was performed with a 25 guage needle by elicitation of paresthesia.

Awareness of cold was tested with ice. Perception of pain to pin-prick was tested over the deltoid. Time to paresis of muscle groups was assessed at the shoulder, elbow and hand. Measurements were made at 30 second intervals by an examiner unaware of group. Postoperatively, temperature, pin-prick and motor function were assessed every 15 minutes until return of function. Data was evaluated by student's T-test.

Results: Both groups were similar demographically. All patients had satisfactory anesthesia to complete surgery. Table 1 displays the times to onset. Onset was more rapid for perception of temperature, pain and paresis at shoulder, elbow and hand in the Study Group. Duration was not statistically different. There were no complications.

Discussion: pH adjustment of mepivicaine appears to hasten onset times to nerve block. This study of interscalene brachial plexus block confirms earlier work of DiOrio with axillary brachial plexus block using mepivicaine.[1] We did not demonstrate the increased duration found by McMorland[3] with bupivicaine epidural blockade. This may be due to sample size.

Alkalinization of mepivicaine appears to safely decrease the interval from injection to adequate surgical anesthesia. Early identification of an acceptable block with no additional morbidity is clearly an advantage of pH adjustment.

References

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Table 1. Onset Times (mean/s.e.m.)

	Sensory (min)		**Motor (min)**		
	Temp	Pin	Shoulder	Elbow	Hand
Control	1.8(.21)	2.7(.35)	3.2(.55)	3.3(.52)	4.2(.53)
Study	1.0(.24)*	1.0(.24)*	0.9(.08)*	0.9(.08)*	1.8(.34)

Study < Control *p < 0.05

Title: NEUROMUSCULAR MONITORING OF THE FLEXOR HALLUCIS BREVIS COMPARED WITH THE ADDUCTOR POLLICIS IN ANESTHETIZED CHILDREN

Authors: M.C. Theroux, M.D,*, B.W. Brandom, M.D., and D.R. Cook, M.D.
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Introduction: Monitoring of neuromuscular blockade is routinely achieved by documentation of adductor pollicis response to ulnar nerve stimulation. Often the hands of small patients are inaccessible during surgery. The flexor hallucis brevis is an alternative site for monitoring of neuromuscular function. However, the relative effects of atracurium at these two sites have not been documented in children. This study was undertaken to compare the effects of this nondepolarizing neuromuscular blocker at these two sites.

Methods: Twenty-four children between the ages of 2 and 18 years having elective surgical procedures under general anesthesia were studied. The study was approved by the Institutional Review Board of the Children's Hospital of Pittsburgh. No children with neurologic or muscular disorders were studied. Choice of anesthetic was left to the attending anesthesiologist. All patients received atracurium. After cleaning the skin with alcohol, 5 surface electrodes were placed over both the wrist and palmar aspect of the hand and over the ankle and medial aspect of the sole of the foot to record ulnar nerve-adductor pollicis and posterior tibial nerve-flexor hallucis responses, respectively. After induction of anesthesia, the nerves were stimulated with supramaximal trains-of-four stimuli (2 Hz for 2 sec at 10 sec intervals). The evoked compound electromyograms were recorded with a Datex NMT monitor. Times to complete loss of neuromuscular function, to 10% and 25% recovery of initial twitch height (as compared to the final baseline), and to the recovery of the train-of-four to 75% (T4/T1 ≥ 0.75) were noted. The data were analyzed by paired t-test with statistical significance accepted at $p < 0.05$. Results are presented as mean ± standard deviation.

Results: Time to complete loss of neuromuscular function was significantly longer ($p < 0.024$) in the flexor hallucis relative to the adductor pollicis (0.69 ± 1.04 min) (see Figure 1). Times to 10% recovery and 10% to 25% recovery of neuromuscular function were similar in the adductor pollicis and the flexor hallucis (n=15). Time to recovery of the T4/T1 ratio to 0.75 was significantly longer ($p < 0.0005$) in the flexor hallucis relative to the adductor pollicis (4.9 ± 5.0 min) (see Figure 2).

Discussion: These results suggest that there is little difference between the posterior tibial-flexor hallucis and the ulnar-adductor pollicis systems in the rate of onset of neuromuscular blockade and early recovery of neuromuscular function in anesthetized children. The statistically significant small delay in onset of complete neuromuscular blockade in the foot relative to the hand could be due to a longer circulation time to the foot. Such a small delay would be of little clinical significance in any non-emergent situation. Hence, either site could be used for clinical monitoring of onset of blockade and early spontaneous recovery. However, if T4/T1 ≥ 0.75 represents adequate, complete, spontaneous recovery, complete recovery is significantly delayed in the flexor hallucis compared to the adductor pollicis in these children. Documentation of delayed recovery, albeit of short duration in the case of atracurium, is justification for questioning the assumption of adequacy of spontaneous recovery of neuromuscular function in the entire body based on assumption of the function of the adductor pollicis only. These results differ from those found previously in adults possibly because more patients were examined (1).

Reference

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* Alfred I. DuPont Institute of The Nemours Foundation, Wilmington, Delaware.

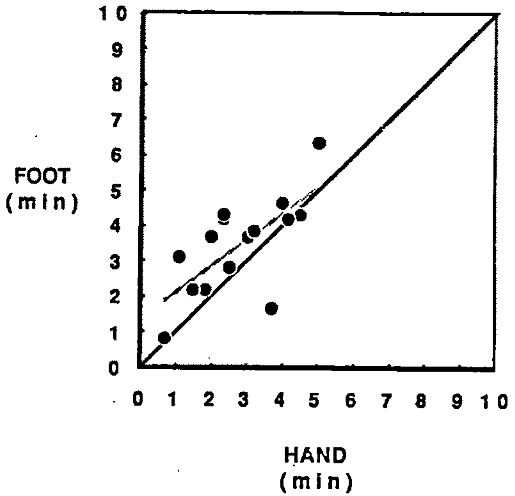

Figure 1. Time to complete loss of neuromuscular function in the adductor pollicis and the flexor hallucis.
----- represents the regression relationship ($Y=0.74X+1.40$, $R^2=0.49$, $N=15$)

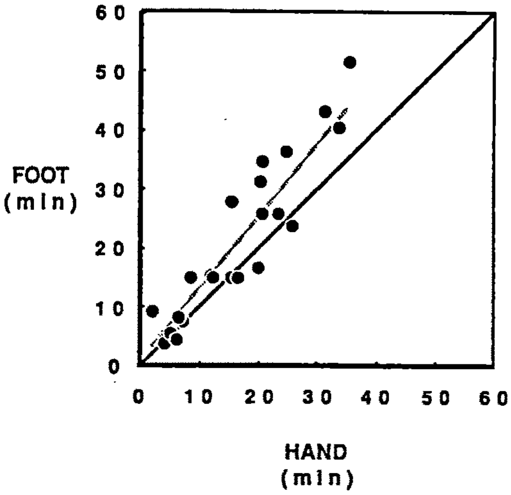

Figure 2. Time to recovery of T4/T1 to 0.75 in the adductor pollicis and the flexor hallucis.
----- represents the regression relationship ($Y=1.23X-0.79$, $R^2=0.83$, $N=22$)

Title: THE INFLUENCE OF FLUMAZENIL ON RESPIRATION AFTER MIDAZOLAM AND/OR FENTANYL.

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Affiliation: Clinic of Anesthesiology (Dir. Prof. G. Kalff) at the
Medical Faculty of Technology, Aachen FRG

Introduction:

After the reversal of Midazolam (Mi) / Fentanyl (Fe) Anesthesia with Flumazenil (Fl) we observed significantly more hypoxemic periods than without antagonisation (1).
Because of this unexpected observation we performed a double blind cross over study in 8 healthy volunteers to inverstigate the influence of Fl versus Plazebo (Pl) on respiratory depression caused by Mi Fe in spontaneously breathy volunteers.

Methods:

After written informed consent and approval by our Institutional Review Board was obtained, the young (20-30 years) and healthy volunteers (8 medical or philosophical students) underwent 4 trials with a time interval of at least 4 days in randomized series:

1. i.v. Mi 0,08 mg/kg BW.
   After 5 min:
   i.v. Fl 0,5 mg.
2. i.v. Fe 0,003 mg/kg BW.
   After 5 min:
   i.v. Fl 0,5 mg.
3. i.v. Mi 0,08 mg/kg BW + Fe 0,003 mg/kg BW.
   After 5 min:
   i.v. Pl = 5 ml NaCl 0,9%
4. i.v. Mi 0,08 mg/kg BW + Fe 0,003 mg/kg BW.
   After 5 min:
   i.v. Fl 0,5 mg.

The oxygen saturation (SAT), respiratory rate (RR) and the sedation were continuously registered using a Ohmeda Pulse Oxymeter and a trained observer. The volunteers reaction to the acustical alarm of the Pulse Oxymeter (SAT < 90%) and the reaction to the investigator's command: "Take a deep breath" were registered. As a measure of respiratory depression we used the area below 90% SAT (Fig 1).

Statistics:

Trial 3 and 4 were compared using the Chi-Square and the U-Test.

Results:

Mi had no servere respiratory effects, Fe caused hypoxemia in 3 volunteers which was not altered by Fl. During the 35 minute observation period, 7 volunteers had hypoxemic periods after Fe and Mi. Fe and Mi caused servere hypoxemia in 7 volunteers. The effects were supraadditive. The areas below 90% as a measure of hypoxemia in 5 minutes intervals are presented in Tab 1. Compared to Mi, Fl reversed the respiratory effects after 1-2 min ($p \leq 0,05$). 5 min after Fl there was no statistical difference any more. Rebound effects were recorded in 7 volunteers between 5 and 20 min after injection of Fl. The trial had to be interrupted with Naloxon in 2 volunteers receiving Fe / Mi and Pl after 15 min because of a prolonged hypoxemia.

Discussion:

1. Mi and Fe have supraadditive effects on respiration which can be antagonized by Fl, but rebound effects are possible. Because trial 3 had to be interrupted in two volunteers it cannot be decided if secondary hypoxemic periods are more pronounced after Fl or the comparabel values after Pl, as we have reported in patient studies.
2. An interaction between Fl and Fe must be considered. It seems to be possible that Fl has a far lower intrinsic effect on the respiratory function than Mi which results in the successful antagonisation of Fe and Mi induced respiratory depression, but still adds to the respiratory depression caused by Fe.

References:

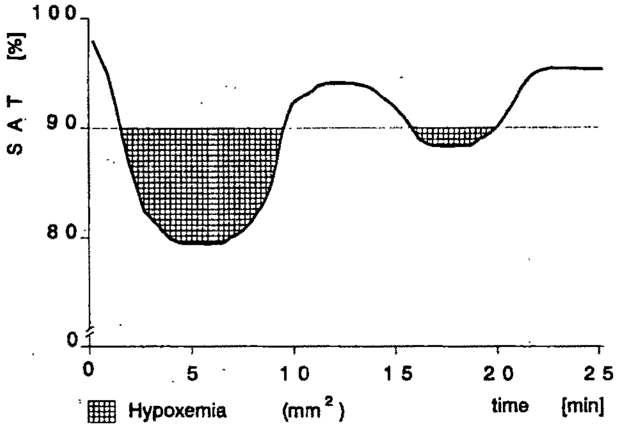
1. Tolksdorf W et al. Anästh Intensivther Notfallmed 1989;24:94-99

Tab 1 Area below 90% SAT after the antagonism of Mi / Fe with Fl and Pl in mm².

	Fl	Pl	Statistics
0- 5 min	220	509	$p \leq 0,05$
5-10 min	249	415	n.s.
10-15 min	240	210	*
15-20 min	149	178	*

* not tested because of the drop out of 2 subjects

Fig 1



Title: THE RESPIRATORY DEPRESSION CAUSED BY FENTANYL IS SLIGHTLY ENHANCED BY FLUMAZENIL.

Authors: W. Tolksdorf, M.D.,Ph.D.; H.O. Prag, M.D.; M. Amberger; M. Vorwold.

Affiliation: Clinic of Anesthesiology (Dir. Prof. G. Kalff) at the
Medical Faculty of Technology, Aachen FRG

Introduction:

Whereas the efficacy of Flumazenil (Fl) on improving vigilance in the presence of other Benzodiazepine Agonist (BZA) is undoubted, its effect on BZA and/or Opioid Agonists (OA) induced respiratory depression is controversely discussed. Some authors describe an improvement of a Midazolam (Mi) induced increase of p_aCO_2 (1) whereas others cannot find an influance on Diazepam induced respiratory depression (2). In two studies using Fl to antagonize Mi / Fentanyl (Fe) Anesthesia we found even worse Oxygen Saturation Values when compared to Plazebo (Pl) (3,4). All our previous studies indicate a slight intrinsic activity of Fl on respiration which can be of clinical importance in the presence of Opioids. We therefore investigated the influence of Fl and Pl on exspiratory pCO_2 and Oxygen Saturation (SAT).

Methods:

15 male, healthy volunteers aged 20-30 years gave written informed consent to participate in this double blind study with crossover design, approved by our Institutional Review Board. All subjects received 3 µg/kg BW Fe + 0,5 mg Fl and one week later 3 µg/kg BW Fe + 5 ml NaCl 0,9% (Pl) i.v., in random order. They were undisturbed and breathed spontaneously.

The following parameters were measured: SAT, pCO_2 and heartrate (HR) continuously, using a pulse oxymeter (SAT, HR) and CO_2 infrared-absorption monitor (Oscar-Fa. Datex). The blood pressure was recorded before and after a 5 min preinjection period (baseline) and at the end of the procedure (25 min). Every minute the degree of sedation was determined by a trained observer. The data were stored up in a microcomputer (Multitalent, Fa. ZAK) and transmitted to a PC after each trial.

Statistics:

The groups were compared with the Wilcoxon rank sum Test. $p \leq 0,05$ is significant.

Results:

The trials could be performed without methodological problems and unwanted side effects of the drugs administered. In trial 1 and 2 there was an increase of pCO_2 and a drop in SAT. The changes of pCO_2 and SAT were more pronounced after Fe + Fl in 12 subjects (80%) compared to 1 subject with the opposite result. 2 subjects showed no difference between trial 1 and 2. The mean differences of SAT and pCO_2 from baseline are presented in fig. 1 and 2. The combination of Fe and Fl caused significantly higher increases in pCO_2 (P=0,007) and more pronounced decreases in SAT (p=0,04), than Fe and Pl.

Discussion:

These results indicate a slight respiratory depressive effect of Fl when combined with Fe. In a previous study it could be shown that Fl antagonizes the respiratory depressive effect of Mi, but not completely back to baseline p_aCO_2 (1). In previous studies respiratory function impaired by Mi + Fe could be improved initially by Fl, but rebound effects on SAT could be observed which were more pronounced than those after Pl (3). The additive or even supraadditive effects of BZA on Opioid induced respiratory depression are well known. When Fe is combined with potent BZAs, such as Mi this effects can partly be antagonized with Fl but because of the slight intrinsic activity of Fl on respiration rebound effects on SAT can be observed 20-40 min later, which may exceed the values of patients who are not antagonized. Therefore a close monitoring of respiratory function in Fl antagonized patients is necessary.

References:

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Fig. 1

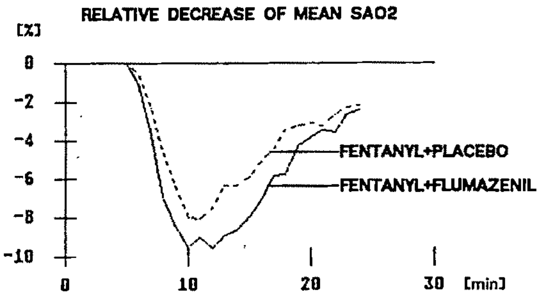
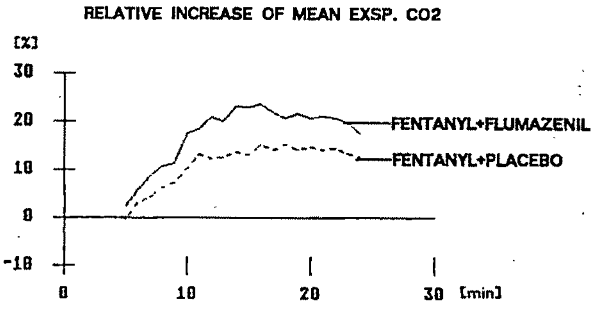


Fig. 2



TITLE: SACRAL EPIDURAL MORPHINE VS. BUPIVACAINE FOR THE RELIEF OF POSTOPERATIVE PAIN IN CHILDREN

AUTHORS: S. K. Tsai, M.D., M. S. Mok, M.D.*, L. F. Hung, M.D., M. Lippmann, M.D.*

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*Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509, U.S.A.

Introduction. Systemic administration of an opiate narcotic is the traditional method of pain relief in children after surgery. However, much interest has been generated in providing postoperative pain relief in children with a regional anesthesia technique. The present study was undertaken to determine the analgesic efficacy and safety of various doses of morphine vs. bupivacaine administered by sacral epidural injection.

Method. Sixty-five (65) pediatric patients with ages ranging from 1 to 12 years and scheduled for abdominal surgery were enrolled into this study after obtaining institutional approval and parental consents. After the patient was anesthetized with general endotracheal anesthesia, the patient was turned to the lateral position and a 5 cm 19G Tuohy needle was introduced into the sacral canal at the S_{2-3} intervertebral space using the loss of resistance technique. After a 10 cm 23G indwelling catheter was introduced into the epidural space through the needle, the needle was removed and the catheter was taped securely in place. At the end of surgery, patients were extubated and taken to the postanesthesia recovery room. In the recovery room when the patients were fully awake from anesthesia, they were divided randomly into 2 groups: Group A (n=33) received epidural administration of bupivacaine 0.25% at 2.5 mg/kg based on ideal body weight, with a maximal dose of 50 mg; and Group B (n=32) received an epidural injection of morphine sulfate with a dose schedule of 1 mg for patients under 7 years of age, 1.5 mg for those 7-10 years, and 2 mg for those over 10 years of age. Pain relief was evaluated with a 5 point objective pain assessment score as described by Krane et al (1) with:

1= Laughing, euphoric
2= Happy, contented, playful
3= Calm or asleep
4= Mild-moderate pain; crying, grimacing, restlessness; can distract with toy, food, parent
5= Severe pain; crying, screaming, uncontrollable

Effect of pain relief, vital signs and side effects were observed for 24 hours after drug administration.

Results. The demographic characteristics and initial pain intensities were similar for both groups. Onset of pain relief with epidural bupivacaine was rapid (within 10 min) and the degree of pain relief was very profound. However, its duration of action was relatively short, lasting only 4-8 hours (6 ± 2.1 hours). On the other hand, sacral epidural morphine provided prolonged pain relief lasting 12-24 hours with an onset time of 15-30 min (fig.). Urinary retention was the major side effect occurring in 30% of the patients with sacral epidural morphine. There was no dural puncture, hypotension or other complications. All patients had satisfactory recovery from the epidural analgesia without neurological sequelae.

Discussion. Sacral epidural block is an easy procedure to perform in children without serious complications. Sacral epidural administration of either bupivacaine or morphine provides effective and safe analgesia in children with postoperative pain. Pain relief produced by sacral epidural morphine has a much longer duration and has surprisingly little side effects in pediatric patients. Hence, it has much to offer in the management of postoperative pain in children and its clinical use should be encouraged.

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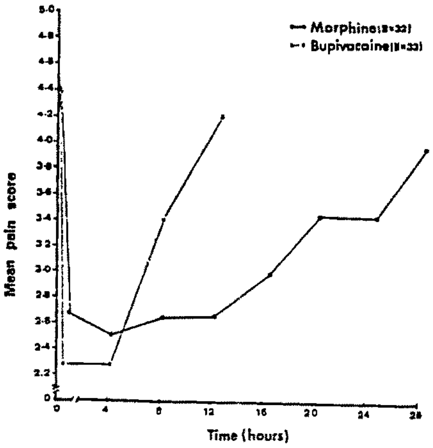

TITLE: SACRAL EPIDURAL ANALGESIA IN CHILDREN

AUTHORS: S. K. Tsai, M.D., M. S. Mok, M.D.*, T. Y. Lee, M.D., M. Lippmann, M.D.*

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Introduction. Epidural administration of a local anesthetic is a widely used form of anesthesia for surgery as well as for postoperative pain control in adult patients. However, this procedure is infrequently performed in children and the dose requirements have been reported to be unpredictable(1). The present study was undertaken to evaluate the efficacy and safety of various doses of bupivacaine by sacral epidural injection for the relief of postoperative pain in children.

Method. Seventy (70) children with physical status ASA I or II and ages ranging from 6 months to 12 years scheduled for lower abdominal surgery were enrolled in this study. Institutional approval and informed parental consents were obtained before their entry into the study. All patients were anesthetized with general endotracheal anesthesia with halothane-N_2O-O_2. At the completion of surgery but before awakening from anesthesia, the patient was turned to the lateral position with both legs flexed. Under aseptic technique, a 5 cm 19G Tuohy needle was inserted into the epidural space through the S_{2-3} interspace which is easily palpable in children. The entry to the sacral epidural space was identified by the loss of resistance technique. By a randomized design, 5 different doses of bupivacaine 0.25% based on ideal body weight were administered. Group A (n=4) received 0.25 ml/kg; group B (n=10) received 0.5 ml/kg; group C (n=25) received 0.75 ml/kg; group D (n=25) received 1.0 ml/kg, and group E (n=6) received 1.25 ml/kg. After drug administration, patients were placed supine and extubated. Upon arrival to the postanesthesia recovery room, when the patient was awake, the level of analgesia was assessed by pinching the skin in a cephalad progression and observing the child's reaction to pain stimulation. Vital signs and adverse effects were also recorded for 12 hours.

Results. There is a good dose response correlation between analgesia and the dose of bupivacaine administered (fig.) except for the 0.25 ml/kg dose which produced ineffective analgesia. For lower abdominal surgery the dose of 1.0 ml/kg appears to provide the best analgesic level (T_{7-9}) and the patients showed no sign or complaint of post-surgical pain for an averaged 6.0 ± 2.1 hours. There was no dural puncture, hypotension or other complications. All patients receiving 0.75-1.25 ml/kg dose of 0.25% bupivacaine had satisfactory recovery and excellent pain relief from the epidural analgesia without neurological sequelae. Grade I motor block was found with the use of 0.25% bupivacaine in all patients except those receiving 0.25 ml/kg dose.

Discussion. Sacral epidural block is an easy and safe procedure to perform in children without complications. With the appropriate dose of local anesthetic administered, it provided excellent pain relief for the postoperative period. Among the different doses tested, 0.75-1.0 ml/kg ideal body weight produced the most suitable level of analgesia for lower abdominal surgery and postoperative pain relief without any observable complication. The sacral epidural injection technique offers an advantage over caudal injection with less dose of medication required, and it is devoid of danger of inadvertent spinal cord injury, hence safer than the lumbar epidural route of injection.

Reference.

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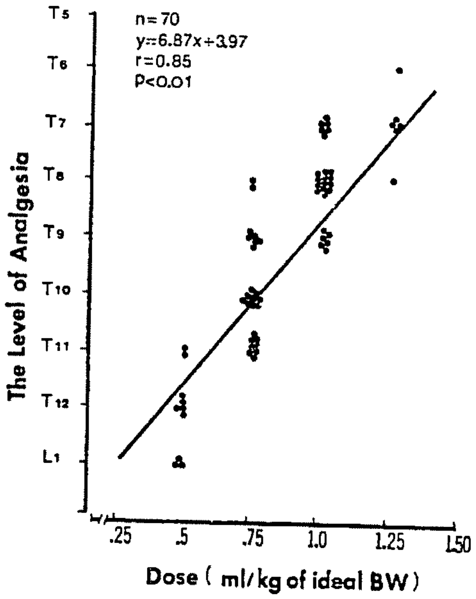

TITLE: DO CALCIUM CHANNEL BLOCKERS DECREASE NEUROLOGIC DEFICITS AFTER INTRACARDIAC OPERATIONS?

AUTHORS: KJ Tuman, M.D., RJ McCarthy, Pharm.D., BD Spiess, M.D., AD Ivankovich, M.D.
AFFILIATION: Department of Anesthesiology; Rush-Presbyterian-St. Luke's Medical Center; Chicago, Illinois

Introduction: Postoperative neurologic dysfunction (PND) remains a serious and often devastating complication after cardiac surgery requiring cardiopulmonary bypass (CPB). The risk of PND is especially high during intracardiac (versus extracardiac) operations, in the elderly and with prolonged CPB time(1). Current options for prophylaxis or therapy of PND are limited in number and documented efficacy. Although previous studies have examined the effect of barbiturates administered before CPB on neurologic outcome after cardiac surgery (2), no corresponding data exists for calcium channel blockers (CCB) in this setting, despite laboratory and clinical evidence that CCB may ameliorate the effects of cerebral ischemia(3). The purpose of this study was to determine the relative importance, if any, of chronic preoperative CCB therapy compared to other factors associated with the risk of PND after cardiac surgery.

Methods: After institutional review board approval, 1878 consecutive consenting adult patients undergoing elective cardiac operations with non-pulsatile hypothermic CPB were prospectively studied. Operations were classified as intracardiac (valve surgery, simultaneous coronary artery and valve surgery, left ventricular aneurysmectomy, repair of intracardiac defects, endocardial mapping procedures) or extracardiac (coronary revascularization). Anesthesia consisted of narcotic-based techniques supplemented with volatile agents as required. The following data was collected: age, gender, type of operation (intra- vs extracardiac), duration of CPB, presence of preoperative dysrhythmias, LV dysfunction, CHF, renal dysfunction, diabetes, preop cerebral disease, recent MI, and need for balloon counterpulsation or hypotension requiring vasopressors after CPB. All cases of PND were verified by a staff neurologist and defined as new focal neurologic deficit or coma associated with focal intracranial injury occurring within the first 24 hours postoperatively. Chronic preoperative CCB therapy was defined as administration for at least 7 days prior to operation and continued until the morning of surgery. The relative influence of the above perioperative variables, including the use of CCB on the outcome variable of PND was tested by multivariate discriminant analysis using the Wilks' Lambda method. Chi-square tests (and T-tests, when appropriate) were used to compare the incidence of PND, as well as the distribution of perioperative variables among groups of patients with or without chronic CCB therapy. The null hypothesis was accepted when p exceeded 0.05.

Results: Multivariate analysis revealed that, for all patients, non-use of CCB was significantly associated with the occurence of PND, preceded only in importance by advanced age, intracardiac operation, and prolonged CPB time. Among patients undergoing extracardiac operations (n=1362), there was no significant difference in the incidence of PND among those who did (n=1012) or did not (n=350) receive CCB (2.1% vs 2.9%, respectively). In addition, non-use of CCB was not a significant multivariate discriminator of the occurrence of PND when considering only extracardiac procedures. In contrast, multivariate discriminant analysis revealed that the most important determinants of PND in patients undergoing intracardiac procedures (n=516), in descending order of importance were:advanced age, prolonged CPB time, non-use of CCB, need for balloon counterpulsation after CPB, diabetes, recent MI, and preop cerebral disease. A significantly lower incidence of PND occurred in the patients undergoing intracardiac surgery who received CCB (n=132) despite being older and having significantly prolonged CPB time compared to those without CCB(n=384,see Table).

INTRACARDIAC PROCEDURES	CCB	No CCB	P value
PND(%)	3.0	8.3	.039
Age(yr.)	64.2±11.7	57.7±15.5	.0001
Gender(%female)	47.0	51.3	.391
CPB time(min)	148±46	134±52	.011
IABP(%)	11.4	6.3	.055
Diabetes(%)	21.2	14.3	.063
Recent MI(%)	23.5	4.7	.00001
Preop Cerebral Dis(%)	8.3	9.9	.597
Need for vasopressor(%)	26.8	22.1	.122
CHF(%)	43.2	49.5	.212
LV dysfunction(%)	73.5	64.8	.068
Renal insufficiency(%)	28.0	22.4	.190
Preop dysrhythmias(%)	51.5	49.2	.647

Discussion: This study suggests that preoperative use of CCB may have a beneficial effect on the occurence of PND in the subset of patients undergoing intracardiac surgery requiring CPB. Although improved neurologic outcome is not a consistent finding in all studies of calcium antagonists during cerebral ischemia, nearly all studies have shown increases in cerebral blood flow and prevention of postischemic impaired reperfusion (3).The finding of a significant interaction between the non-use of CCB and PND for intracardiac operations only, may be related to the finding that PND was 2 to 3 times more frequent than in those undergoing extracardiac procedures, consistent with the hypothesis that the majority of cases of PND after heart surgery are probably related to air or particulate emboli originating within the heart or aorta. As such, the low incidence of PND in those undergoing coronary surgery alone may require a significantly larger sample size to demonstrate such an effect in that subset of patients. Nonetheless, our findings suggest that the improvements in cerebral blood flow and reperfusion seen after use of CCB in other forms of cerebral ischemia may be beneficial in the setting of cardiac surgery and extracorporeal perfusion. Further studies focused on the role of CCB in the prevention of ischemic neurologic injury after cardiac surgery appear to be indicated.

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TITLE: EPIDURAL ANESTHESIA AND ANALGESIA DECREASES POSTOPERATIVE HYPERCOAGULABILITY IN HIGH-RISK VASCULAR PATIENTS

AUTHORS: KJ Tuman, M.D., RJ McCarthy, Pharm.D., BD Spiess, M.D., AD Ivankovich, M.D.
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Introduction: Patients undergoing major vascular surgery for arterial occlusive disease are at high risk for perioperative complications related to atherosclerotic vascular disease (ASVD), such as myocardial ischemia and infarction (MI), as well as peripheral arterial vascular insufficiency (PVI). There is increasing evidence that hemostatic factors play an important role in the pathogenesis of the clinical sequelae of ASVD.(1) Accelerated coagulability, related primarily to increased fibrinogen, factor VII and VIII, and platelet activity, occurs in patients with ASVD and may be accentuated by other factors such as stress, catecholamines, and angiotensin. This study was designed to examine whether perioperative stress produces significant increases in coagulability in such high risk patients, whether postoperative epidural analgesia attenuates any such changes, and whether there is a correlation between coagulation status and the development of postoperative arterial insufficiency (myocardial or peripheral vascular).

Methods: After institutional review board approval, 52 consenting adults were studied. 26 patients with ASVD underwent femoral-popliteal-tibial (n=13) or aortobifemoral (n=13) revascularization, with either general anesthesia combined with epidurally-administered local anesthetic followed by postoperative analgesia using fentanyl and bupivacaine administered via a continuous epidural infusion (GEN-EPI group), or "balanced" general anesthesia using isoflurane, N_2O and fentanyl with parenteral narcotic administration for postop pain relief (GEN). 26 patients without ASVD undergoing non-cardiovascular procedures with "balanced" general anesthesia served as coagulation status controls. None of the patients had any postoperative alterations in coagulation and none were receiving anticoagulant or anti-platelet medications. Intraoperatively, all patients undergoing vascular clamping received 50-75mg heparin reversed with protamine. Postoperatively, no patients received any additional anticoagulation. Estimated blood loss (EBL) was noted; no blood products except PRBC's were administered. Coagulation status was monitored after induction of anesthesia and postoperatively, using thrombelastography (TEG). Measurement of TEG parameters R, K, α, and MA were performed on all samples and compared using ANOVA with repeated measures. The occurrence of ECG evidence of myocardial ischemia, MI and PVI, intraop hypertension, hypotension, and tachycardia, as well as the incidence of preoperative angina, LV dysfunction, CHF, recent MI, diabetes, use of calcium channel or β-adrenergic blockers were compared between GEN-EPI and GEN groups using χ-square analysis; the null hypothesis rejected if $p < 0.05$.

Results: After induction of anesthesia, patients with ASVD had accelerated coagulability compared to controls (larger MA and α). Postoperatively, coagulability did not change in controls, whereas it increased from post-induction in the GEN group (larger MA and α) and decreased in the GEN-EPI group (smaller MA and α). Postoperative coagulability of the GEN-EPI group was similar to the control group.

		GEN	GEN-EPI	CONTROL
Intraop:	R(min)	11.5±3.0	11.8±2.0	12.1±2.9
	K(min)	4.5±.9	5.0±.9	6.7±2.5
	α(deg)	58.0±3.6*	56.8±8.1*	50.8±10.1
	MA(mm)	62.3±4.4*	62.1±5.4*	55.5±8.9
Postop:	R(min)	10.3±.9	11.7±1.9	9.9±2.9
	K(min)	4.2±.8	5.1±1.0	5.9±1.8
	α(deg)	65.4±5.2*§†	50.2±5.7 †	52.6±9.1
	MA(mm)	68.6±3.1*§†	55.2±5.3 †	54.7±6.3

Values are means±SD.
*different from control, §different from GEN-EPI,
†different from intraop, p=0.05 (Tukey-A method)

Postoperatively, 4 of 26 vascular surgery patients developed PVI; 7 developed ECG evidence of ischemia; 3 suffered a postop MI. The occurrence of PVI was significantly greater in the GEN group (4/11 vs 0/15; p=0.047). If postop MI and arterial graft occlusion are considered together as thrombotic events, the number of patients with these events was significantly higher in the GEN compared to the GEN-EPI group (6/11 vs 0/15; p=0.005), despite no significant differences in cardiac risk factors, medications, hemodynamics, duration of surgery, or EBL between groups. TEG revealed significantly accelerated coagulation postoperatively in the 6 patients who developed thrombotic events compared to the 20 patients without thrombotic events (MA: 69.3±4.1 vs 58.4±7.2; α: 66.0±5.9 vs 53.9±8.4; p=0.05), although there were no baseline differences between these groups of patients.

Discussion: The accelerated coagulability seen in the vascular surgical patients in this study is consistent with that reported in medical patients with ASVD; increases in α and MA represent increased fibrinogen-platelet activity. It appears that perioperative stress may accentuate this hypercoagulability in the postoperative period in high risk vascular surgical patients, whereas use of epidural analgesia appears to attenuate this stress response. Previous studies have suggested that improved outcome of major vascular surgery might be achieved using epidural anesthesia/analgesia (EAA).(2,3) Although determinants of outcome after lower extremity vascular surgery are multifactorial, it appears that EAA may influence outcome by decreasing fibrinogen-platelet interaction, which may contribute to improvements in vascular flow by decreasing viscosity as well as the release of factors from platelets which modulate vascular smooth muscle contraction. This study also demonstrates the utility of TEG for detecting such effects on platelet-fibrinogen activity. Further studies of the influence of TEG as a guide for detection and treatment of postoperative hypercoagulability on the outcome of lower extremity vascular surgery are underway.

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Title:
INTRAOPERATIVE HEMODYNAMIC INDICATORS OF MYOCARDIAL ISCHEMIA

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Introduction. Intraoperative myocardial ischemia is associated with postoperative myocardial infarction (PMI). Controversy exists as to whether ECG is an appropriate "gold standard" for assessing myocardial ischemia.^{1} Several hemodynamic indices, including the rate-pressure product (RPP=SBPxHR), pressure-rate quotient (PRQ=MAP/HR), and pulmonary artery pressure have been suggested to be early indicators of intraoperative ischemia. Therefore, we prospectively evaluated coronary artery bypass graft (CABG) patients for intraoperative myocardial ischemia by comparing computer assisted ST-segment analysis with hemodynamic indicators of ischemia.

Methods. Following approval by the Human Investigation Committee, 58 adults scheduled for elective CABG surgery were studied. Prior to induction of anesthesia arterial and pulmonary artery catheters were inserted. All patients were anesthetized with a standardized narcotic anesthetic. All patients were also monitored with the Hewlett Packard Computer processed electrocardiogram ST-segment analyzer model HP 78534L (frequency response of 0.05-100Hz) using leads II and V5. Patients were considered ischemic with new ST-segment deviation ≥ 1mm from their baseline ECG.

A baseline value for the ST-segment, heart rate, blood pressure and pulmonary artery pressure were obtained 5 minutes prior to induction of general anesthesia. Values were recorded at two minute intervals until the initiation of CPB. Each patient's anesthetic was divided into time periods with regard to the following intraoperative events: pre-induction, induction, intubation, 2 min post-intubation, incision, sternotomy, post-sternotomy, aortic cannulation, pre-CPB. All data was stored in a Hewlett Packard Vectra^R computer on a Microsoft Excel^R spread sheet. Patients were followed 72 hours post-operatively for changes in their ECG and elevations in CPK-MB fraction. Data presented as mean ± SD using the Pearson Chi-Square or Fisher's exact test ($p<0.05$) ECG evidence of ischemia was compared with the following hemodynamic indices of ischemia: PRQ<1, RPP>12,000, PAD>18, HR>80, SBP>160, MAP<60.

Results. Nine of fifty-eight (9/58; 15%) patients sustained 46 ischemic episodes pre-CPB. Four of the nine (4/9) were ischemic upon arrival in the OR. Five patients (5/9) became ischemic intraoperatively. In five patients (5/9) the ischemia was initiated by a HR>80 but <100 bpm.

Table I presents the association between ischemic episodes in lead II and V5, and hemodynamic indicators of ischemia. Both a HR>80 and a RPP> 12,000 showed a significant association ($p<0.05$) with ECG evidence of ischemia. The mean RPP during ischemia (11,030) was significantly ($p<0.05$) higher than the mean RPP (7,435) during non-ischemic periods. The PRQ <1 and PAD >18 mmHg also showed a significant correlation with ischemia (10/24 and 11/22) but in 91% of the episodes where the PRQ<1 and 87% of the episodes where the PAD>18 mmHg were without ECG evidence of ischemia. Four patients (4/58) had PMI; 3/4 sustained intraoperative ischemia.

Discussion. Approximately half (46%) of the intraoperative ischemic episodes are not associated with hemodynamic abnormalities; however, in 5/9 patients who were ischemic, the ischemic period was initiated with a HR >80 while the mean HR for all patients pre-CPB was 62±11. Our data showing that an elevated SBP does not correlate with episodes of ischemia while RPP does, demonstrates the dominant role of HR in the development of ischemia. The association of a critical HR and ischemia, is also consistent with our finding that 5/9 ischemic patients had less than a 20% increase from baseline HR at the onset of ischemia. None of the other hemodynamic indices (BP, pulmonary pressures, PRQ) showed significant specificity to be used as an indicator of ischemia. In conclusion, our data suggests that hemodynamic indices cannot be used as "simple" indicators of intraoperative ischemia, since many ischemic episodes occur without significant hemodynamic changes and only small but critical changes in HR.

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Ischemic Periods

ECG Lead	ECG	HR>80	RPP>12,000	MAP<60	SBP>160	PAD>18	PRQ<1
+	24	14*	10*	0	3	11	10
V5 -	784	44	14	31	27	71	105
+	22	12*	11*	1	4	4	11
II -	785	44	13	31	26	78	104

*$p<0.05$

ADDITION OF CLONIDINE POTENTIATES POSTOPERATIVE ANALGESIA OF EPIDURAL SUFENTANIL.

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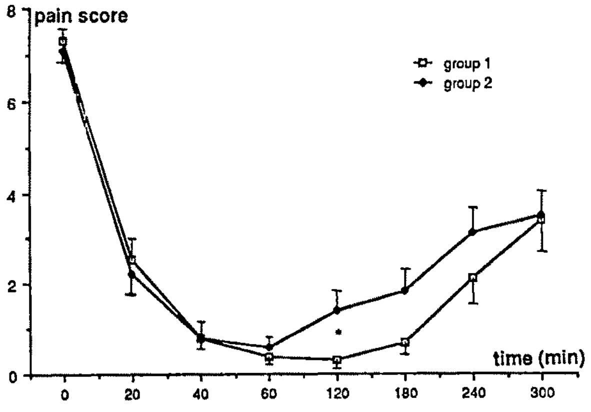
Introduction: Clonidine produces pain relief when administered intravenously, intrathecally and epidurally (1). The aim of this study was to evaluate if clonidine addition would allow a dose reduction of (epidural) opioids while increasing safety and not affecting the quality of analgesia.

Patients and methods: The study was approved by the Hospital Human Investigation Committee and written informed consent was obtained.
40 patients scheduled for abdominal surgery were randomly assigned to receive in a double blind fashion either sufentanil 25 µg with clonidine 1 µg/kg (group 1) or sufentanil 50 µg (group 2) for postoperative pain relief. The top of the epidural catheter was placed at the midthoracic level. General anesthesia was provided with fentanyl 2-5 µg/kg, thiopenthone 3 mg/kg and pancuronium 0.1 mg/kg I.V. Patients were ventilated with a O_2:N_2O (1:1) mixture supplemented with enflurane up to 1%.
As soon as patients recovered and complained about pain (>5 on the visual analogue scale) the epidural injection was given. VAS (0 to 10), systolic and diastolic blood pressure, heart rate, oxygen saturation (Ohmeda Biox 3700 pulse oxymeter), sedation and other side-effects were registered at time 0,20,40, 60 min. and subsequently at one hour intervals. Subsequent doses, administered when the VAS score reached 5, always consisted of sufentanil 50 µg. Results were analyzed statistically using analysis of variance (ANOVA) and the Mann-Whitney-U test.

Results: Both groups were not significantly different regarding age, weight, sex or type of surgery. The onset of pain relief after the first injection was significantly shorter in the 50 µg group (5.8 +/- 0.9 vs 8.8 +/- 1.0 min.) The duration of pain relief (i.e. VAS < 5) was nearly 6 hours, which was not significantly different for both groups.
Regarding the duration of complete pain relief (VAS < 1) the clonidine-sufentanil combination (group 1) appeared to be superior (251.5 +/- 43.7 vs 144.2 +/- 27.5 min.) ($p < 0.05$). This is also reflected in the pain scores presented in Fig.1.
Only 1 patient in each group had a starting value of oxygen saturation below 93%. Oxygen therapy was considered with values lower than 90%. The oxygen saturation remained stable during the first hour in group 1, whereas in group 2, the 50 µg dose induced a significant decrease in oxygen saturation at 10 ($p < 0.001$) and 20 ($p < 0.05$) min. after the injection (88.9 +/- 1.5 and 92.6 +/- 1.0 % resp.). At 30,60, 120 and 180 min. a significant drop of the systolic blood pressure values was noted in the clonidine group. The lowest mean systolic blood pressure value was registered at 60 min. (99.9 +/- 3.0 mmHg). Other side-effects such as sedation, pruritus, urinary retention, nausea and vomiting were not significantly different for both groups. No differences were noticed with respect to onset and duration of pain relief following the subsequent injections. 4 patients of both groups found the second injection superior when compared to the first one. 2 patients of the clonidine groups experienced a better quality of pain relief obtained with the first injection.

Discussion: It has been shown that sufentanil 50 µg epidurally is the ideal dose whereas 25 µg offers pain relief of significant shorter duration (2). The finding that alpha-2 adrenoreceptor agonists had analgetic properties opened new horizons in the treatment of pain. The dose of clonidine required to produce excellent pain relief varies from 2 to 4 µg/kg. A synergistic effect when opioids are combined with clonidine appears to be succesful in terminal cancer care (3). The results in acute pain are very conflicting.
Our study showed that the 25 µg sufentanil dose when combined with clonidine, was superior regarding analgesic quality and duration of complete pain relief. Although the best parameter to monitor respiratory depression is a CO2 response test, monitoring of oxygen saturation showed a dose-related-response. However, hypoxia will be masked or easily corrected by the administration of oxygen, despite the presence or persistence of respiratory depression.
Whereas most authors report hypotension with 2-4 µg/kg, the lack of significant changes of the blood pressure in a study using 3 µg/kg is most surprising (4). It may be concluded that clonidine has a synergistic effect when combined with sufentanil. Therefore it may be possible to lower the dose of sufentanil and decrease the risk of oxygen desaturation. The occurence of serious blood pressure drops is a drawback, forcing us to look for newer opioids or other modifications in order to pursue the objectives of this study.



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Title:

MIDAZOLAM-INDUCED AMNESIA: DOSE-RESPONSE CURVE AND POTENTIATION BY ALFENTANIL

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Introduction: Anterograde amnesia is a well established phenomenon associated with the use of benzodiazepine agents (1,2). However, no dose-response studies are available on benzodiazepine-induced amnesia, and benzodiazepine-opioid interaction with regard to anterograde amnesia is a matter of controversy (3,4). The purpose of the present study was to define the midazolam dose-response curve for anterograde amnesia to a painful event. In addition, we tried to determine whether alfentanil can potentiate midazolam-induced amnesia.

Method: Unpremedicated ASA physical status I or II female adult patients admitted for one day surgery participated in the randomized, double-blind study approved by the Institutional Human Investigation Committee. Patients who had received benzodiazepines or opioids within one month of the investigation were excluded from the study. As an endpoint for amnesia, the absence of recollection of painful pressure on the trapezius muscle 24 hr following the event was used. The painful stimulus was administered with the use of a dolorimeter (Pressure Threshold Meter, PDT Company). The dolorimeter was shown to the patient and the procedure was explained. The pressure against the trapezius muscle was gradually increased, until the patient complained of pain (at least 10 kg/cm^2). The test was performed 60 minutes before the patient entered the operating room and approximately 10 minutes following the insertion of a needle to establish the i.v. line. Midazolam and alfentanil (or saline) were injected 3 and 2 minutes before the test, respectively, and the patient was informed that she had received medications. Twenty four hours following the test, the patients were asked (on the phone) the following questions: "Do you recall the placement of the i.v. line?," "Do you remember receiving any medication in your i.v. line?," "Do you remember what we did right after this?, and "Can you describe it?" Negative (or incorrect) response to the third question was determined as a positive response to the drug.

The study consisted of two groups of patients (midazolam and midazolam-alfentanil), each divided into five subgroups of five patients. Each subgroup received a predetermined dose (midazolam) or predetermined combination of doses (midazolam and alfentanil). The following doses were administered in the midazolam group ($mg \cdot kg^{-1}$): 0.01, 0.02, 0.03, 0.04, and 0.05; the injection was given over 10 seconds and was followed (60 seconds later) by an injection of isotonic saline. In the midazolam-alfentanil group, alfentanil was given in a fixed dose of 0.006 mg kg^1 and midazolam dose varied ($mg \cdot kg^{-1}$): 0.005, 0.01, 0.02, 0.03, and 0.04; both drugs were administered over 10 seconds, first midazolam and, 60 seconds later, alfentanil. The assignment of the patient to one of the ten subgroups was performed randomly. Dose-response curves were determined with the use of probit analysis (5).

Results: Midazolam induced anterograde amnesia in a dose-dependent fashion with the ED_{50} value of 0.023 $mg \cdot kg^{-1}$ (conf. limits: 0.013 and 0.031). The midazolam dose-response curve for amnesia had a flat slope similar to that for unconsciousness, indicating a wide variability in the individual response to the agent with the ED_{05} value of 0.01 $mg \cdot kg^{-1}$ and ED_{95} value of 0.05 $mg \cdot kg^{-1}$. Alfentanil (0.006 $mg \cdot kg^{-1}$) decreased the midazolam ED_{50} value for amnesia from 0.023 $mg \cdot kg^{-1}$ to 0.011 $mg \cdot kg^{-1}$ ($p<0.02$).

Discussion: We have found previously (6) that alfentanil 0.006 $\mu g \cdot kg^{-1}$ decreased midazolam ED_{50} for unconsciousness in a similar population of patients from 0.262 $mg \cdot kg^{-1}$ to 0.125 $mg \cdot kg^{-1}$ ($p<0.001$). This indicates that alfentanil potentiates hypnotic and amnesic effects of midazolam to approximately the same degree. The results suggest that the amnesic effect of midazolam may be secondary to the decreased arousal of the subjects but without producing obvious sedation.

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Title: PATIENT CONTROLLED ANALGESIA (PCA) COMBINED WITH CONTINUOUS INFUSION (CI)

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Introduction: Protagonists of PCA plus CI suggest that the concurrent administration of an infusion of opioids improves the continuity of analgesia for postoperative pain, by maintaining blood concentrations between PCA demands, e.g., when patients are asleep. The purpose of the study was to determine if continuous infusion of morphine contributed to analgesia in patients using a PCA apparatus for postoperative pain.

Method: The effectiveness of morphine after surgery by PCA alone or with a concurrent infusion was investigated in 51 consenting adult patients in a double-blind randomized study design. Prior Institutional Human Investigation Committee approval was obtained. Patients were undergoing major upper abdominal and orthopedic surgery. All three groups received morphine: PCA alone, PCA + 0.5 mg/hr, and PCA + 1 mg/hr for 22 hours postoperatively. An Abbott PCA Plus infuser was used. Initially patients with moderate to severe pain were titrated to a comfort level with a loading dose of 4–6 mg of morphine sulfate (MS). PCA unit dose, 1 mg, interval 8 min. CI was commenced simultaneously with PCA. The assessing study nurse was unaware of which groups the patients were in. Assessments were made at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 10, 14, 18, and 22 hours after commencing PCA. This included pain intensity using a 10 cm visual analog scale (VAS), graded pain relief (0 to 5 scale); sedation (1 – 4 scale) by study nurse. Morphine utilization was calculated in mg/hr for the 22-hour period of observation. Total amount of morphine used was also calculated for each group. An additional (non-randomized) group of 15 patients were also given supplemental M.S. 1 mg per hour in a bolus dose every hour instead of by infusion. Statistical analysis was by analysis of variance and Fisher's protected least significance test.

Results: The groups were similar with respect to age, sex, weight and severity of postoperative pain. Pain intensity, pain relief and sedation were also similar in all three groups. (See Table) The mean dose of morphine used per hour was highest in the CI + 1 mg morphine group, 2.8 mg ($P < 0.05$). In the CI + 0.5 mg group, morphine utilization was similar to PCA only group. The total dose of morphine used per 22 hours was also greatest in the PCA + 1 mg group, 60.4 mg ($P < 0.03$).

The mean morphine utilization comparing day *vs.* night (sleeping) dosage did not differ significantly in any of the groups.

The results of the 15 additional patients who received PCA + 1 mg supplement as an hourly bolus instead of by infusion differed from the other 3 groups only in the period from 6–10 hours after surgery. In this group,decrease in pain intensity, pain relief and sedation were significantly greater than in the 3 other groups for this period. The amount of morphine used was also significantly greater than in the PCA only group for the 22-hour observation period.

Discussion: Results of this study demonstrate that the addition of a constant rate infusion to PCA did not improve the efficacy of analgesia but increased drug utilization when the supplemental infusion rate was 1 mg morphine per hour. Owens[1] demonstrated similar findings with concurrent infusions and suggested that the addition of continuous infusions of morphine to PCA regimes may reduce the inherent safety of this technique. The bolus delivery of 1 mg of morphine hourly demonstrated that this form of drug delivery may have an important effect on pain relief, sedation and morphine utilization.

Table
The Effect of Morphine Infusion Combined with PCA on Postoperative Pain. Mean Score (with S.E.M.) for 22-hour Period

	PCA Only	PCA + CI 0.5 mg/hr	PCA + CI 1.0 mg/hr
Number of patients	n = 17	n = 17	n = 17
Pain intensity (V.A.S.—10 cm.)	4.2 (0.6)	3.1 (0.8)	3.8 (0.6)
Pain relief (0 – 5 scale)	3.0 (0.3)	3.2 (0.3)	2.8 (0.3)
Sedation (1 – 4 scale)	2.4 (0.2)	2.4 (0.3)	2.3 (0.3)
Morphine utilization (mg/hr)	2.1 (0.4)	1.8 (0.4)	2.8* (0.4)
Morphine utilization (mg/22 hrs)	45.5 (4.8)	40.3 (5.1)	60.4* (4.8)

*$P < 0.05$

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Title: MECHANISM OF THE GALLAMINE AND PANCURONIUM INDUCED ELEVATION OF HEART RATE IN GUINEA PIGS

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Introduction. It has been suggested that the acceleration of the heart rate (HR) by gallamine (GAL) and pancuronium (PANC) is due to: (a) prevention of the inhibitory effect of acetylcholine (ACh) on norepinephrine (NE) release mediated through muscarinic receptors located on the sympathetic nerve endings of the sino-auricular (SA) node; (b) prevention of the inhibitory effect of ACh on pacemaker cells; and (c) inhibition of the re-uptake of NE (1,2). In this study the validity of these assumptions has been tested by direct measurement of the effect of GAL and PANC on the electrically evoked release of NE and on the reuptake of NE.

Methods. The excised right atria of g.p. were suspended in Krebs' solution of 37°C aerated with 95% O_2-5% CO_2 and were loaded with ^{3}H-NE. Subsequently the preparations were superfused at the rate of 1 ml/min and 3 ml aliquots were collected continuously. The amount of radioactivity released at rest and after electrical field stimulation (> 10 impulses, 2 ms duration, 1 Hz) administered on 4 occasions (S_1, S_2, S_3, S_4) 18 min apart was measured in the absence of drugs (control) or presence of OXO alone added between S_2 and S_3 or together with atropine (ATROP), GAL or PANC added between S_3 and S_4. In some cases 3 µM ATROP was present in the perfusing solution throughout the experiment. The absolute amount of NE released by S_1, S_2, S_3 or S_4 varied considerably from one preparation to the other. However, the ratios of NE released by consecutive stimuli (e.g. S_2/S_1, S_3/S_2 or S_4/S_3) were quite constant. Therefore, the effect of drugs on the evoked release of NE were determined from the S_n/S_{n-1} ratios. Increase of these ratios indicate facilitation, their decrease inhibition of release. Details of the methods were published (3). Concentrations of antagonists needed to double the concentration of OXO to exert the same effect, were also determined. Significance of data ($p < 0.05$) was evaluated with ANOVA followed by Tuckey's test. The experiments were approved by the Institutional Animal Investigation Committee.

Results. The data summarized in the table indicate that OXO kept in the solution throughout the experiment significantly decreased the release of NE (see table). The inhibitory effect of OXO could be antagonized by ATROP, GAL or PANC as indicated by the increased S_4/S_3 values compared to that obtained with OXO alone. When the presynaptic muscarinic receptors were fully occupied by ATROP, GAL produced a further increase in S_4/S_3 ratios from 0.95±0.05 to 1.13±0.02 ($p < 0.01$). This indicates that in addition to muscarinic inhibition GAL also prevents reuptake of NE. ATROP 6.3 nM, GAL 158 nM or PANC 126 nM added to the perfusing solution required the doubling of the concentration of OXO to obtain the same inhibition of NE release. These concentrations are similar to those present in the plasma with the clinical use of these compounds.

Conclusions. It has been demonstrated by direct measurement of the evoked release of NE that GAL and PANC similarly to ATROP antagonize the inhibitory effect of muscarinic receptor stimulation (by ACh under physiological and by OXO under experimental conditions) on NE release. This effect of GAL and PANC together with the inhibition of reuptake of NE and inhibition of the postsynaptic muscarinic receptors (4) located on the cells of the SA node is probably responsible for the elevation of the heart rate observed with the clinical use of these compounds. Vecuronium (10 µM, pipecuronium (50 µM) and d-Tc (100 µM) failed to inhibit the effect of OXO and did not enhance NE release. These data are in agreement with the clinical effect of these compounds on heart rate.

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Table. Effect of Atropine, Gallamine and Pancuronium on the Oxotremorine Induced Inhibition of NE Release

(All values are means±SEM of 5 experiments)

	S_2/S_1	S_3/S_2	S_4/S_3
Control (No Drug)	0.97±0.03	0.99±0.02	0.96±0.02
Oxotremorine*	0.97±0.03	0.24±0.03‡	0.91±0.08§
Oxotremorine† +Atropine	0.97±0.05	0.23±0.05‡	4.52±0.78¶
Oxotremorine† +Gallamine	0.96±0.02	0.21±0.02‡	5.42±0.67¶
Oxotremorine† +Pancuronium	0.98±0.02	0.24±0.03‡	2.51±0.10¶

*0.5 µM OXO was added between the second (S_2) and third (S_3) stimulation period and was present during the rest of the experiment.

†ATROP (0.3 µM), GAL (70 µM) and PANC (1 µM) were added between S_3 and S_4.

‡Indicates significant difference from control.

§An S_4/S_3 ratio close to unity indicates that the inhibitory effect of OXO on NE release was maintained.

¶Indicates significant difference from OXO alone.

TITLE: EPIDURAL ANESTHESIA AND INTRATHORACIC BLOOD VOLUME IN DOGS

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Introduction

Decreases in rib cage muscle tone caused by high epidural anesthesia (EA) should reduce both total intrathoracic volume (V_{th}) and the functional residual capacity (FRC), a measure of the amount of intrathoracic gas at end-expiration. However, most studies of supine humans have demonstrated little effect of EA on FRC (1). The cardiovascular effects of EA may be one of the factors responsible for this apparent preservation of the FRC. If intrathoracic blood volume concurrently decreases with the onset of EA, FRC may be unchanged, despite a decrease in V_{th}. In support of this hypothesis, Arndt et al (2) demonstrated using whole-body scintigraphy that intrathoracic blood volume decreased during EA in supine humans; FRC was not measured. To investigate how changes in intrathoracic blood volume caused by EA may affect lung volumes, we administered high EA to 5 anesthetized dogs lying supine. V_{th} at end-expiration was measured using a high-speed 3-dimensional x-ray scanner and the amount of gas in the thorax at end-expiration (the FRC) was measured using nitrogen washout techniques. With this information shifts in intrathoracic blood volume caused by epidural anesthesia could be calculated.

Methods

This study was approved by the Institutional Animal Care and Use Committe. Five dogs (8 to 13 kg) were anesthetized with sodium pentobarbital. After endotracheal intubation, an epidural catheter was placed percutaneously though the vertebral arch of the second coccygeal vertebra and advanced until the tip was near the L4-L5 level. Electromyogram electrodes (silver hooks) were implanted in several rib cage and abdominal muscles to monitor the motor level of blockade. The dogs were placed in the Dynamic Spatial Reconstructor (DSR), a high speed x-ray scanner that uses the computed tomography principle to provide 3-dimensional volume images of the thorax (3). Scans at end-expiration were obtained during spontaneous breathing, and the FRC measured immediately afterwards in duplicate using a nitrogen washout technique. Etidocaine 1.5% (total dose of 8.8 ± 2.4 mg/kg [M ± SD]) with 1:200,000 epinephrine was injected to abolished electrical activity of all rib cage and abdominal muscles, so that the dogs were breathing only with the diaphragm. DSR scans and FRC measurements were repeated at end-expiration. During data analysis, DSR images were processed to provide a three-dimensional image of the thoracic cavity. V_{th} was measured by counting the number of volume picture elements within the thoracic cavity. Thoracic tissue volume (V_{tis}), which included intrathoracic blood volume, was calculated as the difference between V_{th} and FRC.

Results

EA consistently increased V_{th} (mean increase of 76 ± 35 ml). This increase in V_{th} was caused by approximately equal increases in both V_{tis} and FRC (Table 1), so that the percentage of V_{th} comprised of gas was similar before (46 ± 8%) and during (47 ± 5%) EA.

Discussion

Pentobarbital-anesthetized dogs lying supine demonstrate considerable expiratory activity in rib cage and abdominal muscles (3), so that end-expiratory V_{th} is less than V_{th} during relaxation of the chest wall muscles. Paralysis of the rib cage and abdominal muscles increased V_{th} by abolishing this expiratory activity. However, the increases in V_{th} caused by high EA were accompanied by increases in V_{tis}, so that changes in gas volume (FRC) were minimized, and the percentage of the thoracic volume occupied by gas remained remarkably constant. The increase in V_{tis} was probably caused by increases in intrathoracic blood volume. The decrease in intrathoracic blood volume with the onset of EA noted by Arndt et al (2) may reflect a lower dermatomal level of block (T_{4-5}) or species differences. Also, human subjects lying supine do not demonstrate expiratory muscle activity, so that these results are not directly applicable to humans. Nevertheless, these results show that during EA changes in total intrathoracic volume are not identical to changes in thoracic gas volume, and that changes in V_{tis} must be considered when describing the effects of anesthesia on lung volume.

Table 1.–Changes in thoracic volumes caused by epidural anesthesia (ml)

	Before epidural			During epidural		
Dog	FRC	V_{tis}	V_{th}	FRC	V_{tis}	V_{th}
1	417	375	792	456	425	881
2	308	425	733	339	452	791
3	195	366	561	283	409	692
4	249	281	530	281	310	591
5	440	400	840	465	415	880
mean	322	369	691	365	402	767
±SD	106	54	139	90	54	125

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Supported in part by research grants HL-04664 and GM/HL-40909 from the National Institutes of Health.

Title: ETIOLOGIES AND INCIDENCE OF ACUTE PULMONARY EDEMA IN THE IMMEDIATE PERIOPERATIVE PERIOD

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Introduction: Episodes of acute pulmonary edema in the immediate perioperative period are infrequently reported, and the incidence and epidemiologic characteristics of these events need further elucidation. Therefore, we reviewed our experience with acute pulmonary edema occurring intraoperatively or in the immediate postoperative recovery area in 139,245 patients receiving general anesthesia for non-cardiac surgical procedures from 1985-1988 to determine its incidence and etiologies.

Methods: With appropriate institutional approval, we identified all cases of documented acute pulmonary edema occurring intraoperatively or in the immediate postoperative recovery area in patients undergoing general anesthesia for non-cardiac surgical procedures from 1985-1988. These patients were identified by integration of institutional data bases that contain demographic and anesthetic, surgical, and medical outcome information on over 200,000 patients who received anesthetic services during this time period. During the study's duration, all patients were monitored at or above the "Standards of Monitoring" adopted October, 1986 by the American Society of Anesthesiologists. Acute pulmonary edema was defined as the rapid development of pink, frothy sputum, hypoxemia, and fluffy infiltrates on chest roentgenogram, with or without clinical findings of rales or wheezing. Identified episodes were analyzed as sentinel events, with retrospective review of medical records and, when indicated, interviews with anesthesia personnel associated with specific occurrences.

Results: There were 20 episodes of acute pulmonary edema in 139,245 patients (1:8,350). These episodes can be categorized into six presumed etiologies:

1) Overtransfusion of a patient with normal cardiac function - occurred in four patients, undergoing emergency surgery for acute gastrointestinal bleeding. Rapid volume replacement early in the procedure for hypovolemia was required in each case.

2) Relative overtransfusion of a patient with diminished cardiac function - occurred in two patients, both undergoing minor surgical procedures of ≤ 30 min duration. Both patients had previous hospitalizations for congestive heart failure and left ventricular ejection fractions ≤ 25%, estimated by echocardiography. Fluid volume administered intraoperatively prior to onset of edema averaged 225 ml.

3) Negative intrathoracic pressure associated with laryngospasm - occurred in five patients, ranging in age from 14 to 73 years. All occurred after endotracheal extubation and laryngospasm that required paralysis and reintubation.

4) Transfusion-related acute lung injury (TRALI) - occurred in five patients who received intraoperative transfusion of whole blood or blood products. Granulocyte antibodies in the serum of at least one donor unit were identified in all cases.

5) Excessive intranasal phenylephrine given to facilitate nasotracheal intubation - occurred in three young, healthy patients undergoing oral surgical procedures. In these three cases, a commercially-prepared 1/2% phenylephrine solution in a pliable bottle was administered to the patients while they were in a supine position and the bottle was inverted for application. When squeezed, the inverted bottle delivers a volume of approximately 3 ml, in contrast to 0.1 ml when held upright in the manufacturer's recommended position. The excess of phenylephrine elevated systemic resistance sufficiently in each case to cause transient left ventricular failure and pulmonary edema.

6) Tachyrhythmia after administration of neuromuscular blockade reversal agents - occurred in two middle-aged patients who received neostigmine and atropine iv simultaneously for reversal of neuromuscular blockade. The doses were neostigmine 1 and 3 mg and atropine 0.4 and 1.2 mg, respectively. Both developed a supraventricular tachyarrhythmia greater than 200 bpm, precipitating acute pulmonary edema.

None of these twenty patients died within six months of their procedure. Further, none had serious pulmonary sequelae, although three required mechanical ventilation > 24 hrs. In general, patients had rapid improvement within 12 hours with oxygen supplementation, with or without assisted ventilation, diuresis, and, in some, inotropic support.

Discussion: Our incidence of pulmonary edema was 1:8,350 (0.0012) compared to 1:4,500 reported by Cooperman and Price[1] in their series from 1957-1969. We were not surprised to find several cases involving overtransfusion in patients with and without normal cardiac function. Several of the other etiologies were, however, unexpected or occurred more often than expected. Pulmonary edema after laryngospasm is infrequently reported, particularly in adolescents and adults.[2] It is usually believed to result from forced inspiration against a closed glottis, inducing large negative intrapleural and transpulmonary pressure gradients and causing transudation of fluid from capillaries in the lung interstitium. TRALI is typically characterized by the development of hypoxemia and pulmonary edema, often within two hours of transfusion of whole blood or blood products that have granulocytic or lymphocytic antibodies. In most cases, there is resolution of the acute lung injury with four days.[3] The discovery of three young patients undergoing oral surgery who developed pulmonary edema after receiving excessive amounts of intranasal phenylephrine led to changes in our practice to eliminate further similar occurrences.

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Title: EPIDURAL OPIOID ANALGESIA DOES NOT ALTER THE NEURO-ENDOCRINE RESPONSE TO THORACOTOMY

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Introduction: Epidural anesthesia and analgesia have been shown to modulate the neuro-endocrine response to surgical stress (1). We sought to investigate whether epidural opioid analgesia alone can modify the hormonal stress response to thoracotomy compared with intercostal conduction blockade. Additionally, we have assayed serum prolactin concentrations to assess the role of this hormone in the stress response.

Methods: After obtaining approval from the Massachusetts General Hospital Subcommittee for Human Studies thirty-one patients undergoing thoracotomy for lobectomy or pulmonary wedge resection were randomized into two groups. Group 1 patients were to receive epidural fentanyl via continuous infusion throughout the perioperative period. Group 2 patients would be given intra- and postoperative intercostal bupivicaine blocks.

After obtaining written consent, all patients were premedicated with diazepam 5-10mg P.O. one hour prior to arrival in the operating room. Patients randomly assigned to Group 1 next had placed a lumbar epidural catheter. A 5ml test dose of lidocaine 1.5% with epinephrine was used to aid in determining correct catheter placement. An arterial catheter was placed in all patients and other monitors were used as stipulated in the Harvard monitoring guidelines. General anesthesia was next induced in each group using sodium thiopental 3-4mg/kg, vecuronium 0.1mg/kg and enflurane in oxygen. Prior to the thoracotomy incision, Group 1 patients were given 100μg fentanyl in 10-15ml preservative-free saline epidurally. Epidural fentanyl was then infused at the rate of 50μg/hr (10μg/ml) throughout the perioperative period. Prior to emergence, those patients randomized to Group 2 were given intraoperative intercostal blocks. Postoperatively, Group 1 patients were maintained on the epidural infusion. If necessary, additional amounts of epidural fentanyl were administered if the patient report- or appeared in pain. Similarly, those patients randomized to Group 2 received supplemental intercostal bupivicaine blockade (5ml/rib-0.5%) throughout the postoperative period.

Blood samples were obtained at the following times: 1) Preoperative; 2) One hour post-thoracotomy incision; 3) Emergence from general anesthesia; and 4) Postoperative day one at 9:00AM. Serum cortisol and prolactin concentrations were determined using sensitive and specific radioimmunoassays.

Results: The serum cortisol concentrations are shown in Table 1.

Table 1: Serum cortisol (nmol/L); Mean ± S.E.

Time pt.	Overall	Epidural	Intercostal
1	545±52 (n=31)	446±70 (n=17)	645±77 (n=14)
2	985±53 (n=29)	938±72 (n=16)	1032±50(n=13)
3	1281±52(n=31)	1205±70(n=17)	1358±77(n=14)
4	826±61 (n=22)	863±77 (n=14)	789±102(n=18)

Statistical analysis (ANOVA - Newman-Keul's Range Test): We noted significant differences($p<0.05$) between time points 1 and 2 and 3 and 4 for all groups; however, no significant difference was noted between the epidural and intercostal groups at any time points (Table 1).

Serum prolactin concentrations are shown in Table 2.

Table 2: Serum prolactin (ng/ml); Mean ± S.E.

Time pt.	Overall	Epidural	Intercostal
1	10.1±2.6(n=31)	14.7±4.3(n=18)	7.9±1.2(n=14)
2	46.1±6.2(n=29)	54.9±9.1(n=16)	35.3±7.1(n=13)
3	28.5±3.4(n=31)	32.8±5.4(n=17)	23.0±3.3(n=14)
4	12.4±2.1(n=22)	14.1±3.3(n=14)	9.4±1.2(n=18)

We noted significant differences($p<0.05$) between time points 1,2 and 3. No significant differences existed between time points 1 and 4, and there were no differences between intercostal and epidural groups (Table 2).

Serum prolactin concentrations for males and females are shown in Table 3.

Table 3: Serum prolactin (ng/ml); Mean ± S.E., all groups.

Time pt.	Male	Female	p
1	6.4±0.7 (n=21)	19.9±8.5 (n=8)	.015
2	36.6±4.5 (n=4)	71.0±12.0 (n=8)	.011
3	24.7±3.9 (n=22)	39.2±6.1 (n=8)	.062
4	8.9±1.1 (n=18)	28.0±6.8 (n=8)	.0001

Conclusions: A) Serum cortisol concentration is greatest at the time of emergence from general anesthesia. There is no significant difference between epidural opioid analgesia and intercostal conduction blockade at any time point in the serum cortisol concentrations. B) Serum prolactin concentrations are significantly increased at time points 2 and 3. Again, there is no difference between groups. C) Female patients have a higher serum prolactin concentration at all time points.

Discussion: Clearly, in the dose and volumes of epidural fentanyl used, no statistically significant differences between the two groups was seen. We may also conclude that epidural opioids do not modulate the neuro-endocrine response to thoracotomy incision. At time point 2, epidural opioids have been administered, but intercostal blocks have yet to be performed. As can be seen, no difference exists between the epidural opioid patients or the control (intercostal) group. Prolactin has been identified as a possible modulator of the hormonal stress response (2). We report statistically significant increases in serum prolactin concentrations both intraoperatively and upon emergence from anesthesia. Of interest is the observation that prolactin concentrations peak early in the operative course, while cortisol concentrations rise later at the time of anesthetic emergence. Perhaps, prolactin represents an early mediator of the stress response to surgical insult. In summary, we have shown that in doses adequate to produce acceptable patient analgesia, no difference was seen in the hormonal stress response in patients receiving epidural opioid analgesia or intercostal conduction blockade. Additionally, we have shown that epidural fentanyl does not modify the stress response to thoracotomy compared to control. Lastly, we have provided some evidence that prolactin may be an early stress hormone.

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Title: THE TIME-COURSE AND DOSE-RELATED EFFECTS OF HALOTHANE ON THE INTRAOCULAR PRESSURE OF ANESTHETIZED CHILDREN

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Introduction. Accurate intraocular pressure measurements (IOP) are essential for the diagnosis and treatment of congenital glaucoma, but often require heavy sedation or general anesthesia in children (1). In adults a variety of induction agents are associated with a reduction in the IOP (2). Halothane has been reported to have a dose-dependent effect on the IOP.(1) We studied the effects of (i) time and (ii) an increase in the end-tidal halothane concentration to determine the optimal timing for IOP measurements in children anesthetized with halothane and nitrous oxide.

Methods. After obtaining approval of the institutional Human Studies Committee and written informed consent from the parents, we studied 80 healthy unpremedicated ASA 1 or 2 children scheduled for elective strabismus surgery. In 30 children IOP was measured at 1 min intervals, immediately after induction of anesthesia and return of the eyes to a neutral midline position. In these patients the oropharyngeal end-tidal halothane (et-halo) and nitrous oxide (N_2O) concentrations were kept constant during the measurements.(3) Although there were interpatient variations in the et-halo, the concentration for a given patient was held within ± 0.05% during this phase. In another 50 children, IOP was measured immediately after induction, after 10 mins at a steady state end-tidal halothane concentration of 0.5% and 1.0% in 66% N_2O, and immediately after tracheal intubation, which was facilitated by 0.5 mg/kg atracurium. A repeated measures ANOVA and the Student's paired "t" test were used for statistical analysis, with each eye being considered separately.

Results. In the 30 patients studied in phase 1, there were no signficant differences in the intraocular pressures measured minute-by-minute, while the end-tidal halothane and N_2O concentrations were kept constant (Fig 1). There was no significant correlation between IOP and et-halo concentration expressed as a percentage or in age-appropriate MAC multiples. The 50 patients studied in phase 2 were divided into 3 groups; below 2.5 years, 2.5-7 years and 7-12 years. There were no signficant differences between the IOP measured at 0.5 or 1% halothane in any of the three age groups or in pooled data. However tracheal intubation in all age groups was associated with a signficant rise in IOP. (Table 1)

Discussion. Postinduction IOP measurements have been reported to be lower than preinduction values (1,2). If halothane caused a reduction in the IOP in our patients, it occurred between induction and return of the eyes to the midline, as the IOP remained stable over the next 10 mins. The stability of the postinduction IOP was noted in all patients, even though these were interpatient variations in the et-halo. However, there was no correlation between IOP and et halo. Furthermore, IOP was not affected by increasing the et-halo from 0.5 to 1.0%. Apparent reductions in IOP following induction may be secondary to elevated baseline readings in struggling children rather than a drug effect of halothane. (4,5) We conclude that IOP measurements should be performed at any time in the 10 min after induction, but before tracheal intubation.

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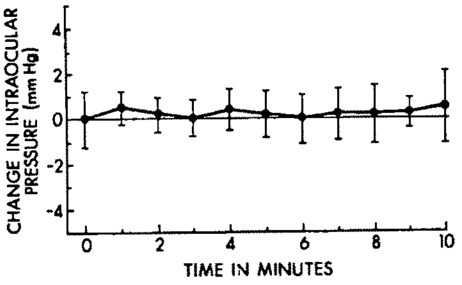

TABLE 1

Age Range (years)	Numbers of eyes	INTRAOCULAR PRESSURE (Mean ± SEM) mmgHg			
		Baseline	0.5% halothane	1.0% halothane	Post-ET
0.5-2.5	30	8.0 ± 0.9	8.4 ± 0.9	8.5 ± 0.9	16.1 ± 1.1*
2.5-7	52	9.4 ± 0.5	10.8 ± 0.4	10.8 ± 0.4	18.8 ± 1.0*
7 - 12	18	11.9 ± 2.0	12.3 ± 1.5	11.3 ± 1.9	20.1 ± 1.8*
Total	100	9.3 ± 0.53	10.2 ± 0.43	10.0 ± 0.42	17.7 ± 0.77*

*$P < 0.05$ Post ET IOP vs baseline, 0.5% and 1% halothane

Title: DOES THE INTRACEREBRAL INJECTION OF DIBUTYRYL 3',5' CYCLIC ADENOSINE MONOPHOSPHATE
REVERSE HALOTHANE ANESTHESIA?

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Introduction A pharmacologic agent that reverses inhalational anesthesia will provide, aside from potential clinical applications, insight into the mechanism of general anesthesia (GA). Previous studies report a return of righting reflex when halothane anesthetized rats receive intracerebral injections of a cyclic adenosine monophosphate (CAMP) congener (1). We designed a system to study this phenomenon in the goat in order to determine whether intraventricular (IV) dibutyryl CAMP (dbCAMP) reverses inhalational GA.

Methods Following approval by our Animal Care Committee, five goats were mask anesthetized with halothane, intubated and mechanically ventilated with a halothane-oxygen mixture to a constant end-tidal CO_2 (30-35 mmHg) and halothane (1.3-1.4%) concentration. End-tidal gases, arterial, central venous and intracranial pressures, raw EEG, ECG and rectal temperature (RT) were monitored continuously and the lateral ventricles were cannulated. Power spectrum analysis of EEG data provided a measure of total brain electrical activity (TBA) with units mVolt/sec. Arterial blood gases and neurologic exams were performed every 30 minutes. One hour after induction of general anesthesia 1 cc of mock CSF was injected over 1 minute into the right horn of the lateral ventrical. Incremental intraventricular injections of dbCAMP began one hour later and comprised 50-100 mg doses each dissolved in 1 ml mock CSF, injected over 1 min and repeated every 15-30 min until a response was obtained (dose range 100-300 mg). Radiolabelled microsphere injections for determination of regional cerebral blood flow were made prior to and after induction and after mock and final dbCAMP injections. Immediately after the last microsphere injection the goat was sacrificed and the ventricular cannulae injected with methylene blue to confirm cannulae location.

Results Prior to induction, all goats had normal heart rate, mean arterial pressure (MAP) and RT. After induction of GA heart rate and MAP decreased appropriately (to 60-80 bpm and 50-70 mmHg) and remained constant until the final injection of dbCAMP. Cortical (C-) and subcortical (SC-) CBF (34.4± 3.1 and 27.9 ± 3.4 ml/100g/min, respectively) were unchanged by GA (Fig 1). Neurologic exam revealed negative corneal reflexes, constricted pupils and no response to tail clamp. Mock CSF injection caused no significant changes in vital signs, TBA, CBF, or neurologic exam. Three to five minutes after the final dbCAMP injection, heart rate increased to 160-180 bpm and MAP to 150-180 mmHg. IV dbCAMP significantly increased CBF in all regions and this value was significantly greater for SC-CBF (207.3±7.1) than C-CBF (92.0±7.4); 95% confidence limits determined by repeated measures ANOVA. GA reduced TBA in the high frequency range (12-30 Hz) by more than one-third while IV dbCAMP increased this parameter more than fivefold from awake values in all goats. Fig 2 shows high frequency TBA vs time in goat #3. Ten to fifteen minutes after the final dbCAMP injection all goats demonstrated spontaneous hyperventilation, swallowing, nasal flaring, eye opening and head movement. Neurologic exam following IV dbCAMP revealed positive corneal reflexes, dilated pupils and negative tail clamp response. During IV injections intracranial pressure transiently rose approximately 10 mmHg and methylene blue injection confirmed IV location of all cannulae.

Discussion Our findings indicate that after IV injection of dbCAMP halothane anesthetized goats exhibit behavioral and metabolic evidence of arousal without reversal of analgesia. The constellation of clinical signs occuring after dbCAMP injection may represent antagonism of the hypnotic component of general anesthesia or activitation of a CNS excitatory system. CAMP is a well known intracellular messenger with many sites of actions (2) and continued investigation of the effects of cyclic nucleotides on GA may aid in elucidating the molecular mechanisms of both anesthesia and arousal.

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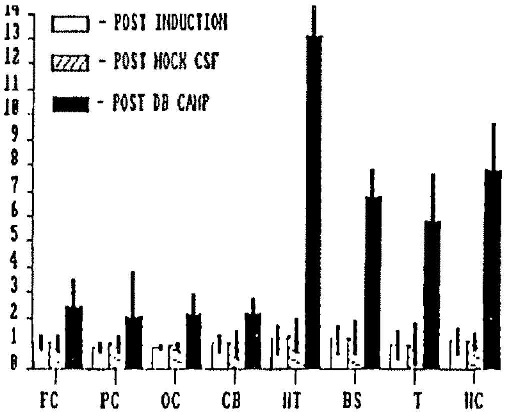

Fig. 1. Regional cerebral blood flow: multiple of awake value. FC, PC, OC are frontal parietal and occipital cortices, respectively; CB, cerebellum; HT, hypothalamus; BS, brainstem; T, thalamus; HC hippocampus.

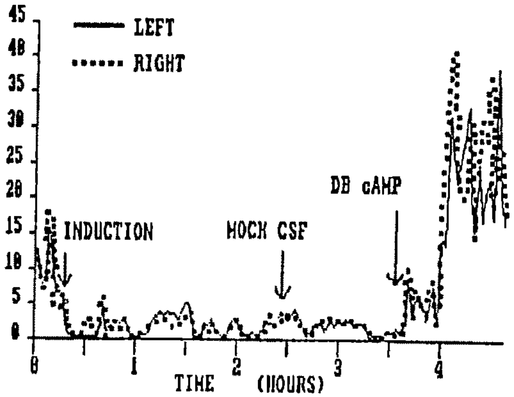

Fig. 2. Brain activity in 12-30 Hz range (mVolt/s)

The effects on muscle tone of selective alpha-2 adrenergic agonists and antagonists during high-dose alfentanil anesthesia in the rat

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INTRODUCTION. Dexmedetomidine (DMED) is a new, potent and selective, alpha-2 adrenoceptor agonist which produces analgesia, sedation, and bradycardia;[1] effects similar to those seen after opiate administration. However, in rats, coadministration of DMED with alfentanil (ALF), does not potentiate the cardiorespiratory depression commonly associated with the highly potent opiate (unpublished data). One unique property of DMED is its ability to produce muscle flaccidity. In previous work, we demonstrated that pretreatment of rats with DMED prevented ALF-induced rigidity.[2] The present study was designed to answer two questions: First, can DMED be used to treat rather than prevent opiate-induced rigidity? Second, will the subsequent administration of atipazemole, an alpha-2 antagonist, result in a reversal of DMED's effects without adverse increases in ALF-induced rigidity?

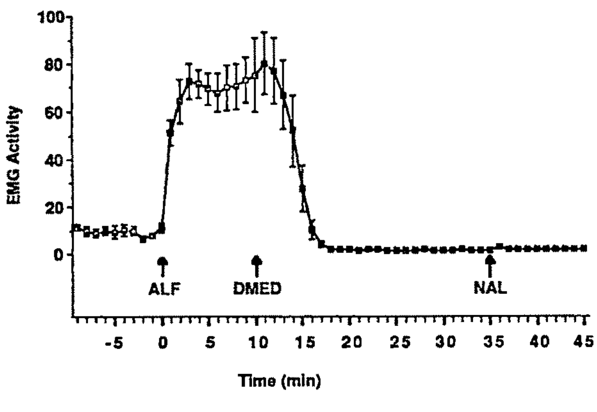
METHODS. The subjects were 20 male Wistar rats (220-320gm). The study was approved by our Animal Care Committee.

In **Experiment 1**, 8 rats were studied to determine the effects of DMED on established ALF rigidity. Baseline electromyographic (EMG) activity was measured over 15 min and then each animal received ALF (0.5mg/kg sc). EMG activity was recorded for an additional 10 min and then DMED (30μg/kg sc) was injected. After 25 min of EMG recording, naloxone (NAL,1mg/kg sc) was administered and data were collected for 10 min more.

In **Experiment 2**, 12 rats were studied to determine the consequences of atipazemole on DMED's antagonism of ALF-induced rigidity. Observers were blinded as to drug treatment identity. Baseline EMG activity was recorded for 15 min and then each animal received ALF (0.5mg/kg sc). 10 min later rats received DMED (30μg/kg sc) and after 12 min of EMG recording, rats were injected with atipazemole (1mg/kg sc). 15 min later, NAL (1mg/kg sc) was injected and EMG activity was recorded for a final 10 min. For both experiments the EMG activity was continuously integrated and the resultant RMS values were calculated each minute. Data were analyzed using one-way ANOVA and significant differences over time within groups were determined with Newman-Keuls *a posteriori* tests. Data were expressed as mean±SEM and $P<0.05$ was considered statistically significant.

RESULTS. Baseline values were not significantly different among rats in either experiment. In **Experiment 1**, ALF resulted in a significant increase in EMG activity within 1 min (**Figure 1**). The increased EMG activity correlated with subjective hindlimb rigidity. Administration of DMED (10 min after ALF) resulted in a marked decrease in EMG activity in every rat, becoming statistically significant 6 min after DMED. Thereafter, EMG activity remained at or below pre-ALF baseline. NAL injection 25 min after DMED had no apparent effect on the already low EMG activity.

Experiment #1



In **Experiment 2**, ALF also produced rigidity in every rat. However, in contrast to Experiment 1, DMED significantly decreased EMG activity (within 10 min) in only 8 of the 12 animals (**Figure 2**). There was no apparent technical reason for the complete lack of response in the 4 animals. In the DMED responders, atipazemole injection produced a marked increase ($P<0.05$) in EMG activity within 7 min. The rigidity after atipazemole was not significantly different from that seen prior to DMED. The subsequent NAL administration resulted in a marked decrease in EMG activity to levels indistinguishable from baseline ($P<0.05$).

DISCUSSION. The results of Experiment 1 suggest that DMED may be clinically effective for treatment as well as prevention of muscle rigidity induced by highly potent opiates like ALF. However, the reasons for the subsequent failure of 30% of the animals in Experiment 2 to respond to DMED was not readily apparent. There was no evidence for technical difficulties in the experiments involving the nonresponding animals. Further studies must be conducted to determine if pharmacokinetic, genetic, environmental, or other unknown factors play a role. Nevertheless, data from responding animals in Experiment 2 demonstrate that atipazemole-reversal of DMED in the presence of high-dose opiate anesthesia will result in a re-expression of muscle rigidity. A significant rebound rigidity or other visible adverse consequences of atipazemole administration could not be demonstrated in this study. These experiments add to the essential pre-clinical knowledge base necessary for the introduction of these new alpha-2 drugs to clinical anesthesia. Alpha-2 agonists show increasing promise as adjuvants to opiate anesthesia.

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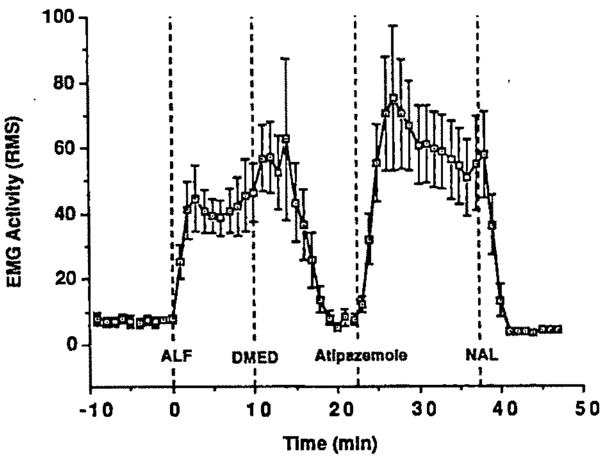
Experiment #2



Title: CARDIOVASCULAR ACTIONS OF DESFLURANE (I-653) IN HUMANS

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Introduction. Desflurane (I-653) is a new inhaled anesthetic, chemically similar to isoflurane, but with advantageous lower blood (1) and tissue (2) solubilities, and little or no metabolism (3). In swine the cardiovascular effects of desflurane do not differ from those of isoflurane (4). The present study extends these investigations to humans. Our results reveal important differences between desflurane and isoflurane in their circulatory effects.

Methods. We obtained approval of our committee on human research, and informed consent. Using local anesthesia, venous, radial arterial, and thermodilution pulmonary arterial cannula were placed in six male volunteers (age 23 ± 0.7 years; weight 76.4 ± 4.7 kg). The volunteer rested quietly, in a dimly lit room. We waited an additional period until heart rate, systemic and pulmonary arterial blood pressures, and cardiac output remained unchanged for 10-15 min. Anesthesia was induced with desflurane in oxygen and the trachea intubated, without administration of other drugs. Ventilation was controlled to maintain normal arterial PCO_2. Core temperature was controlled at 36.8 ± 0.0°C. Cardiovascular variables measured awake were measured again after fifteen minutes of stable end-tidal concentrations (measured by infra-red spectroscopy) of 1.0, 1.5, and 2.0 MAC desflurane. Data were compared using paired-t tests with a Bonferroni correction. Statistical significance was accepted at $P < 0.05$ (corrected).

Results. Desflurane caused dose-dependent decreases in systemic vascular resistance (SVR), stroke volume (SV), and mean systemic arterial blood pressure (BPa) and increases in central venous pressure (CVP) (figs 1 and 2). Heart rate (HR) did not change at 1.0 MAC, but increased at 1.5 and 2.0 MAC (fig 4). Cardiac output decreased at 1.0 MAC, but was not statistically different from the conscious value at 2.0 MAC (fig 3).

Discussion. Desflurane (I-653) is chemically similar to isoflurane, and in swine their cardiovascular actions are indistinguishable (4). The cardiovascular depressant efffects of desflurane we observed in humans have some differences from those seen in swine, and from those previously observed with isoflurane in humans (5). In humans, desflurane causes less decrease in systemic vascular resistance and mean arterial blood pressure than does isoflurane. In contrast to isoflurane, desflurane does not increase heart rate at 1.0 MAC; heart rate at 1.5 and 2.0 MAC appear to be similar for the two anesthetics. While cardiac output at 1.0 MAC isoflurane is unchanged, it is decreased by 16% with desflurane. In contrast, at 2.0 MAC desflurane cardiac output is unchanged from the conscious value, while at an equipotent concentration of isoflurane it is decreased by 11%. We conclude that in addition to the advantages of lower blood and tissue solubilities, more rapid emergence from anesthesia (6), and little or no metabolism, desflurane possesses the further advantage of lesser undesirable cardiovascular effects: absence of heart rate increase at light levels of anesthesia, and lesser decreases in systemic vascular resistance and mean arterial blood pressure, with maintainance of cardiac output at near conscious levels even at high anesthetic concentrations.

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Data are mean±S.E. * indicates $P < 0.05$ vs. conscious

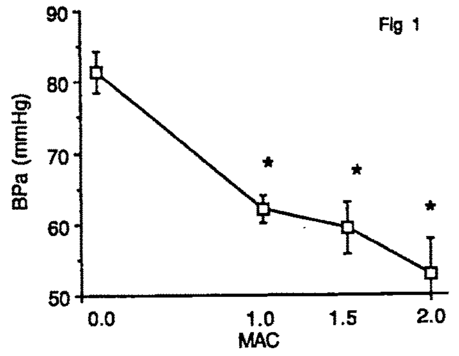
Fig 1

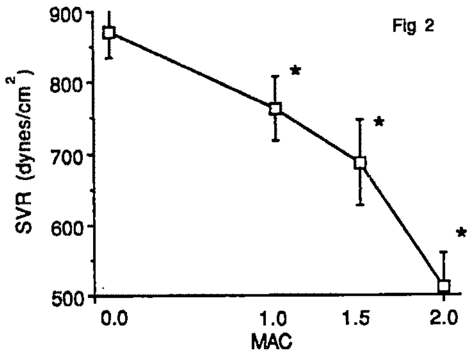
Fig 2

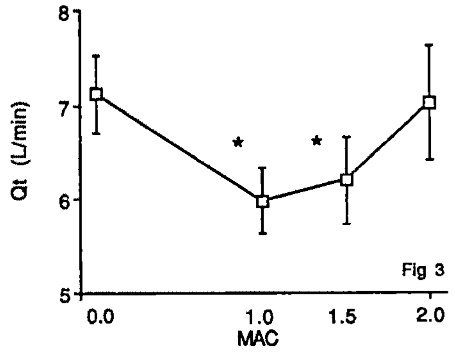
Fig 3

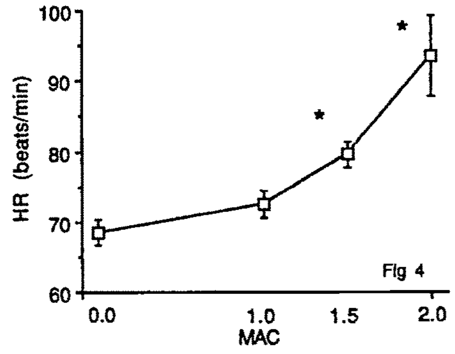
Fig 4

Title: DURATION OF ANESTHESIA INFLUENCES THE CARDIOVASCULAR ACTIONS OF DESFLURANE (I-653)

Authors: RB Weiskopf, MD, MK Cahalan, MD, N Yasuda, MD, EI Eger II, MD, P Ionescu, MD, IJ Rampil, MD, S Lockhart, MD, J Caldwell MD, MA Holmes, AB, B Freire, BS, BH Johnson, MS, M Laster DVM, S Kelley, MD

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Introduction. Desflurane (I-653) is a new inhaled, halogenated anesthetic, differing from isoflurane by replacement of the single chlorine atom by a fluorine atom. The result is lesser blood (1) and tissue (2) solubilities. Isoflurane is the only modern, halogenated, inhaled anesthetic, not associated with circulatory changes with increasing duration of anesthesia (3). Cardiovascular changes with duration of anesthesia have been associated with halothane (4-5), fluroxene (6), and enflurane (7). We tested whether cardiovascular variable changes with prolonged desflurane anesthesia in humans.

Methods. We obtained approval of our committee on human research, and informed consent. Using local anesthesia, venous, radial arterial, and thermodilution pulmonary arterial cannula were placed in six male volunteers (age 23 ± 0.7 years; weight 76.4± 4.7 kg). Anesthesia was induced with desflurane in oxygen and the trachea intubated, without administration of other drugs. Ventilation was controlled to maintain normal arterial PCO_2. Core temperature was controlled at 36.8 ± 0.0°C. Cardiovascular measurements were made during the first hour of anesthesia, after fifteen minutes of stable end-tidal desflurane concentrations (measured by infrared spectroscopy) of 1.0 and 2.0 MAC desflurane. Measurements were repeated during the seventh hour of anesthesia, at the same anesthetic concentrations. Data from the first and seventh hours of anesthesia were compared using paired-t tests. Significance was accepted at $P<0.05$.

Results. Cardiac filling pressure (central venous pressure; CVP) and mean systemic and pulmonary arterial pressures did not change with prolonged anesthesia at either anesthetic concentration. Stroke volume did not change with prolonged desflurane anesthesia, at either anesthetic concentration. However, systemic vascular resistance (SVR) decreased 24% at 1.0 MAC and by a statistically insignificant 13% at 2.0 MAC desflurane (fig 1). Heart rate (HR) (fig 2) and cardiac output (Qt) (fig 3) increased equally with prolonged anesthesia at both 1.0 and 2.0 MAC.

Discussion. All inhaled halogenated anesthetics cause cardiovascular depression. Some of the depression observed during the first hour of anesthesia is lessened or abolished after several hours of anesthesia, with all inhaled halogenated anesthetics except isoflurane. Although desflurane is similar chemically to isoflurane, and its cardiovascular actions in swine (8) and humans have many similarities to those of isoflurane, the return of cardiovascular function with prolonged duration of desflurane anesthesia more closely resembles the changes seen with halothane, enflurane, and fluroxene. These effects of duration of anesthesia appear to be related to changes in systemic vascular resistance. After several hours of anesthesia, a further decrease in resistance is associated with cardiac output increases, and, with desflurane, cardiac output returns to a value not different from when the volunteers were conscious. Price et al (5) prevented the changes seen with prolonged halothane anesthesia by the administration of a β-antagonist, and accordingly attributed this recovery phenomenon to anesthetic activation of β-receptors. However, prolonged enflurane anesthesia (7) does not change heart rate despite decreased SVR and increased cardiac output, stroke volume and dP/dt. Similarly, in another study (4), heart rate after five hours of halothane anesthesia did not differ from that of the first hour of anesthesia. Because isoflurane undergoes less metabolism that does halothane, enflurane or fluroxene, it has been suggested that cardiovascular recovery may be related to metabolism (3). Our data do not support this concept, because desflurane undergoes little or no metabolism (9), yet demonstrates cardiovascular changes similar to those seen with metabolized halogenated anesthetics. Thus, although we have demonstrated cardiovascular changes with prolonged desflurane anesthesia, the mechanism for this phenomenon is not clear.

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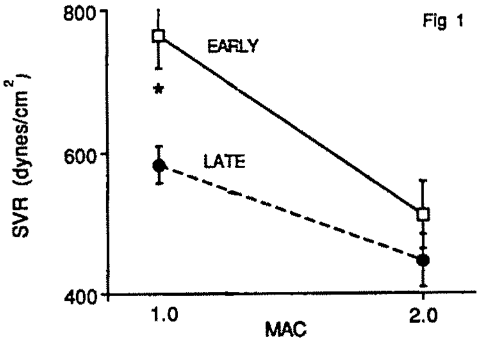

Fig 1

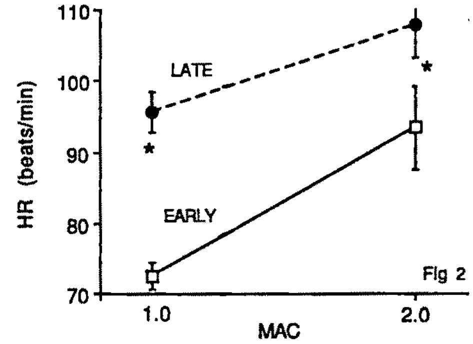

Fig 2

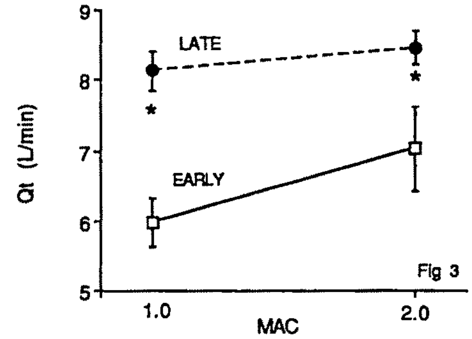

Fig 3

Data are mean±S.E. * indicates $P<0.05$, early vs. late

Title: THE OXYGEN CONSUMPTION - OXYGEN DELIVERY RELATIONSHIP IN ICU PATIENTS: AN ANALYSIS

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Introduction: Much investigation has explored the relationship between O_2 delivery (DO_2) and O_2 consumption ($\dot{V}O_2$) in the critically ill (1,2,3). Such patients, especially those with the adult respiratory distress syndrome (ARDS), exhibit "delivery-dependent $\dot{V}O_2$" wherein increases in DO_2 result in increases in $\dot{V}O_2$, implying a metabolic oxygen debt. This is in contrast to the normal situation where $\dot{V}O2$ does not increase further when DO2 exceeds a critical point (330 ml/min/kg (3)). These observations are valid only at rest. However, in only a few reports is it stated that patients were at rest, or sedated and paralyzed. Further, in ARDS oxygen extraction ratios (ER, $\dot{V}O_2/DO_2$) are lower than in other critical situations, such as congestive heart failure (4).

This study involving ICU patients examines $\dot{V}O_2$, DO_2, and ER at rest and during ICU interactions that increase $\dot{V}O_2$ (5). The aim was to determine (a) whether critically ill patients increase ER and/or DO_2 during periods of increased metabolic demand and (b) is there a difference in the $\dot{V}O_2$-DO_2 relationship between rest and activity?

Methods: Nine mechanically ventilated critically ill surgical ICU patients were studied on 14 occasions. Each study consisted of at least two resting and three activity periods, one being a chest physical therapy (CPT) session. CPT is known to enhance $\dot{V}O2$ by about 50% (5). Being at rest was defined as lying quietly with eyes open able to react to surrounding events (5). Continuous measurements of VO2 were made with the gas exchange method using a Datex Deltatrac (Sensormedics, Anaheim CA). This instrument has been validated *in-vitro* using a test lung system (6) and found to be accurate within ±5%. During the study several simultaneous samples of arterial and mixed venous blood were obtained and analyzed for O_2 saturation (SO_2) with an IL-282 co-oximeter and for PO_2 using an IL 1312 blood gas analyzer. Hemoglobin (Hg) was measured using a Coulter counter. Calculations:

O_2 content (CO_2)= Hg x SO_2 x 1.34 + 0.003 x PO_2
ER = (CaO_2 - $C\bar{v}O_2$)/(CaO_2) DO_2 = $\dot{V}O_2$/ER
Cardiac output (CO) = $\dot{V}O_2$/($CaCO_2$ - $C\bar{v}O_2$)

This study was approved by the IRB.

Results:

	$\dot{V}O_2$ ml/min	DO_2 ml/min	ER	CO l/min
Rest	218±41	781±154	0.28±0.04	5.8±1.5
ACT	247±43*	863±187*	0.29±0.05	6.6±1.6
CPT	312±72*	949±183*	0.33±0.06*	7.2±1.8

*Significantly different than rest (P< 0.25)
ACT: activity other than CPT (e.g moving limbs)
Fig. 1 $\dot{V}O_2$-DO_2 relationship for all data points
Fig. 2 $\dot{V}O_2$-DO_2 relationship at rest, during CPT and other activity (ACT).

Discussion: In the specific patient population studied, DO_2 and ER increased (the latter in all patients except one) to meet the 50% increase in $\dot{V}O_2$ during CPT. This is consistent with the up to 3-fold ER increase seen in exercised normal subjects. At lower levels of ICU activity (~ 15% increases in $\dot{V}O_2$) ER did not increase significantly although DO_2 did. Figure 1 contains all data points and demonstrates what appears to be a delivery dependent pattern. However, when the results are grouped according to rest or activity state, as seen in Figure 2, the dependence of $\dot{V}O_2$ on DO_2 at the higher levels of DO_2 and $\dot{V}O_2$ are mainly due to CPT and ACT. These results indicate that the activity state should be taken into account when evaluating the $\dot{V}O_2$-DO_2 relationship in ICU patients. This relationship is clincally important because the ability to vary ER is vital in maintaining $\dot{V}O_2$ in the face of fluctuating DO_2. Guitierrez et al.(1) observed that patients with a fixed ER as DO_2 and $\dot{V}O_2$ decreased had a 70% mortality, while those whose ER increased had only a 30% mortality. More study is needed to determine whether the magnitude of change in ER in relation to that in $\dot{V}O_2$ during routine ICU interactions has any prognostic significance in the critically ill.

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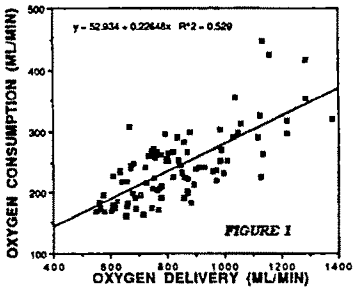

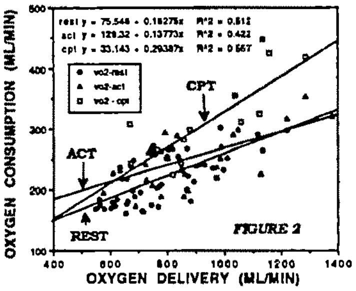

Title: LOWER ESOPHAGEAL CONTRACTILITY IS SUPERIOR TO CLINICAL SIGNS FOR CONTROLLING ALFENTANIL INFUSIONS

Authors: R. Wender, M.D., E. Harow, M.D., K. Park, B.A., R. Saunders, M.D. and A. Zaentz, M.D.

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Introduction. Previous studies have described methods for the continuous infusion of narcotics in combination with nitrous oxide.[1-3] Infusion techniques have been based on clinical signs and/or pharmacokinetic drug properties. Recently, a method for controlling alfentanil infusions using lower esophageal contractility (LEC) was developed.[4] The present study tested the hypothesis that LEC is superior to traditional clinical signs for controlling alfentanil infusions during alfentanil/nitrous oxide anesthesia.

Methods. With Investigational Review Board approval, we studied thirty ASA I and II patients aged 19-66 years scheduled for lower abdominal gynecologic surgery of 45 min - 3 hr. duration. Patients were premedicated with midazolam 2-5 mg IV. Following a 20-25 mcg/kg alfentanil bolus, anesthesia was induced with sodium thiopental 3-5 mg/kg. Succinylcholine 1 mg/kg was used to facilitate endotracheal intubation, and muscle relaxation was accomplished with vecuronium, pancuronium, or atracurium. Ventilation was controlled to maintain P_{ET} CO_2 at 35 ± 3 mm Hg. Anesthesia was maintained with N_2O 70% and a continuous alfentanil infusion initially set at 1.0 mcg/kg/min.

Patients were assigned to one of two groups. For group L (LEC controlled) patients, the alfentanil infusion rate was varied according to the following criteria: If the esophageal contractility index[5] (ECI) was less than 30 for nine minutes, the infusion rate was decreased by 0.25 mcg/kg/min.; if the ECI was greater than 120 for six minutes, a 7.5 mcg/kg alfentanil bolus was administered and the infusion rate was increased by 0.25 mcg/kg/min. For group C (clinical signs controlled) patients, the infusion rate was varied according to the investigator's observations of traditional clinical signs (Heart Rate (HR), Systolic Blood Pressure (SBP), sweating, tearing, etc.). The investigator was blinded to LEC monitoring. For both groups, if HR exceeded 100 bpm and/or if SBP exceeded 160 mm Hg, the investigator intervened with appropriate administrations of alfentanil, calcium channel or beta-adrenergic blockers, or an inhalational anesthetic agent.

SBP (via oscillotonometry), HR (via ECG lead II), ECI, and alfentanil infusion rates were recorded every three minutes by an observer. Alfentanil was administered with a Model 900 Harvard Mini Infuser (Bard). LEC was measured using the Lectron 302 monitor and probe (American Antec). The following variables were selected as determinants of superiority for controlling the alfentanil infusion: alfentanil dosage (ALF), the number of therapeutic interventions made by the investigator (INTERV), the number of times HR and SBP exceeded acceptable limits (i.e., 100 bpm and 160 mm Hg) (EXCEED), and the time from reversal of muscle relaxation to spontaneous respiration (SPON). Statistical comparisons were made between groups using the Student's T-test. A value of $p < 0.05$ was regarded as significant.

Results. (See Table). There were no significant differences in patient age, weight, or length of surgery between groups. All data shown in the Table are mean ± SD. The average alfentanil infusion rate, the number of therapeutic interventions, and the frequency of undesirable hemodynamic events were all statistically greater for Group C. Including alfentanil infusion rate manipulations, Group C patients required 120 therapeutic interventions, whereas Group L required 43. Group C patients exceeded the hemodynamic limits 51 times compared with 12 times for Group L. There was no significant difference between groups in times from reversal of muscle relaxation to spontaneous respiration.

Discussion. The pharmacokinetic properties of alfentanil allow for its continuous infusion in combination with nitrous oxide to produce satisfactory general anesthesia. Previous studies have controlled the infusion rate by observing patient signs (somatic, hemodynamic, and sympathetic) of inadequate anesthesia[1,3] or by monitoring LEC.[4] The purpose of this study was to compare these two infusion techniques and determine which is superior.

This study revealed that controlling alfentanil infusions with LEC results in significantly less drug usage, significantly fewer therapeutic interventions, and significantly better hemodynamic control. Both the patient and the anesthesiologist benefit from use of this technique. Thus, LEC is superior to traditional clinical signs for controlling alfentanil infusions during alfentanil/nitrous oxide anesthesia.

TABLE

	n	ALF* (mcg/kg/hr)	INTERV* (#/hr)	EXCEED* (#/hr)	SPON (min)
Group L	15	60 ± 12	2.1±1.3	0.6±1.4	2.4±1.5
Group C	15	78 ± 32	4.8±2.9	2.6±3.4	3.5±1.8

* Statistically significant difference between groups

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Title: VECURONIUM ATTENUATES ICP INCREASES DURING ROUTINE TRACHEOBRONCHIAL SUCTION

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Introduction

Beside hyperventilation, adequate sedation is applied to mitigate the difficulties with control of intracranial pressure (ICP) during tracheobronchial suction (TBS). Nevertheless, brisk bucking and coughing may occur during TBS. The aim of this study was, therefore, to evaluate the routine use of an intermediate-acting muscle relaxant before TBS and to quantify the degree of neuromuscular (nm) blockade necessary to prevent unacceptable increases in ICP due to diaphragmatic movement.

Methods

After institutional approval, 9 patients (mean age: 37 years; mean body weight: 71.5 kg) with moderate increases in ICP (19.2±7.6 mm Hg) due to head injuries or spontaneous subarachnoidal bleeding were investigated. Heart rate, mean arterial pressure, endexspiratory CO2 and ICP (epidural probe; Gaeltec^{R}) were continuously monitored and recorded on an integrated data bank (HP 758534 A^{R}). All patients were ventilated and sedated with midazolam-sufentanil. Ventilation was adjusted to maintain a paCO2 of 30±2 mm Hg. Each patient served as his own control. A) After a bolus dose of propofol 0.5 mg/kg, routine TBS was performed without the use of muscle relaxants. B) 4 hours later, before the next TBS, the ulnar nerve was stimulated at the wrist in every patient, and the response of the add. poll. muscle was recorded using the Accelograph (Biometer^{R}) nm transmission monitor. Train-of-four (TOF) stimulation was used every 15 sec. After supramaximal stimulation had been achieved, a bolus dose of vecuronium 0.12 mg/kg (ED95x2) was given intravenously. When the response to TOF stimulation had disappeared, a 50 Hz tetanus was applied for 5 sec, and nm blockade was quantified using the posttetanic count (PTC; 1). Afterwards, TBS was carried out as described before. Subsequent increases in ICP were recorded and cerebral perfusion pressure (CPP) was determined. Diaphragmatic movements, bucking and coughing were registrated by visual observation and graded as absent, slight, moderate or severe.
Statistical analysis was performed by students t-test for paired data; $p < .05$ was regarded as significant. Values are expressed as mean ± SD.

Results

Heart rate, mean arterial pressure and paCO2 remained unchanged during the whole investigation. No statistically significant differences were seen in baseline ICP (18.2±7.4 vs. 20.2±8) during both investigation periods. Moderate to severe bucking and coughing were observed in all patients during TBS without muscle relaxation. ICP increased significantly from 18.2±7.4 to 24±8.1 mm Hg, and CPP decreased from 68.9±11.2 to 62.4±8.2 mm Hg ($p < .05$). After the bolus dose of vecuronium, a PTC of 5.4±5 (range: 0-15) was observed 4.2±1.2 min (range: 3.6) later. Slight diaphragmatic movement could be elicited only in 2 patients (PTC 12 and 15) during TBS. ICP (20.2±8 vs. 20.1±7.6 mm Hg) and CPP (64.9±12.9 vs. 64.8±12.8 mm Hg) remained unchanged (Table).

Discussion

Tracheobronchial suction is a potent trigger for diaphragmatic movement by reflex activation of the phrenic nerve. Despite continuous sedation, controlled hyperventilation and stable hemodynamics, significant increases in ICP were observed without the use of nondepolarizing muscle relaxants. Further decreases in CPP in patients with already compromised cerebral dynamics were the consequence.
Vecuronium was utilized for nm blockade in this study because of its lack of cardiovascular side effects, rapid onset and intermediate duration of action (2). The diaphragm is less sensitive to nm blocking drugs than peripheral muscles (3). As demonstrated in the study, intense nm blockade quantified by PTC is necessary to rule out any bucking or coughing, i.e. to ensure total diaphragmatic paralysis in response to tracheal stimulation. A PTC of at least 5 is necessary to prevent any impact of diaphragmatic movement on ICP.
In conclusion, deliberate muscle relaxation with an intermediate-acting nondepolarizing muscle relaxant (vecuronium; ED95x2) is imperative in patients with compromised cerebral dynamics 4.2 min before routine pulmonary management.

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Table Effect of diaphragmatic movement on ICP and CPP without (A) and after nm blockade with vecuronium 0.12 mg/kg (B) during TBS; n=9

	ICP		CPP	
	control	TBS	control	TBS
A	18.2±7.4	24.0±8.1*	68.9±11.2	62.4± 8.2*
B	20.2±8.0	20.1±7.6	64.9±12.9	64.8±12.8

Mean values in mm Hg ± SD; * $p < .05$ to control

Title: **THE EFFECTS OF ANGIOTENSIN-INDUCED ARTERIAL HYPERTENSION ON CANINE CEREBRAL BLOOD FLOW VELOCITIES IN CORRELATION TO CEREBRAL BLOOD FLOW**

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Introduction: Cerebral blood flow (CBF) is kept constant over a wide range of cerebral perfusion pressure by control of cerebral autoregulation (1). However, intravenous and volatile anesthetics, cerebrovascular disorders or chronic arterial hypertension may lead to impairment or a shift of the cerebral autoregulatory response (2). Measurement of blood flow velocities (BFV) in basal cerebral arteries by transcranial Doppler sonography (TCD) may be of value in assessing cerebral hemodynamics where CBF-measurements cannot be performed routinely (3). The present study was designed to determine whether changes in regional (rCBF) and global cerebral blood flow (gCBF) can be correlated to changes in TCD-obtained cerebral blood flow velocities during excessive arterial hypertension in dogs.

Methods: This protocol was approved by the institutional animal care committee. 10 male foxhounds (weight: 24±3 kg) took part in the study. After induction of anesthesia (premedication: ketamine 5mg/kg im, thiazine 8-10 mg im; anesthesia: etomidate 4-11 mg iv) and tracheal intubation, ventilation was set to control end-tidal CO_2 in the range of 33-37 mmHg ($petCO_2$, Capnomac™). Anesthesia was maintained by continuous infusion of etomidate (1.5 mg/kg/h), 67% nitrous oxide in oxygen and supplemented by fentanyl and vecuronium for surgical preparations. The inferior vena cava was cannulated for drug administration and central venous pressure measurements (CVP, mmHg). Mean arterial blood pressure (MAP, mmHg) was measured via the left femoral artery and a single lumen pig-tale left ventricular catheter was placed under pressure curve control via the contralateral femoral artery. CBF-measurements were performed by left-ventricular injection of nonradioactive colour-coded microspheres ($5x10^7$, diameter 11.9±1.9 μm; injection time: 15 sec) and reference blood sampling via the femoral artery (7.5 ml/min). 1.5-2 g tissue samples from frontal, parietal and occipital cortex, vertex area and brainstem were excised and digested following removal of the brain at the end of the experiment. The numbers of blood and tissue microspheres were counted in an improved Neubauer hematocytometer. CBF calculations and sample processing were performed like described elsewhere (4). Systolic (Vsyst, cm/sec) and mean BFV (Vmean, cm/sec) were monitored by a pulsed transcranial Doppler system (TC2-64 B™) with a range-gating mechanism and flow direction discrimination. Following a small craniotomy at vertex area, which is, in contrast to humans, necessary due to complete absorption of the ultrasonic beam, the TCD-probe (8MHz) was placed on the dura mater, adjusted in a clamp to provide constant insonation angle and insonation depth and focussed on the basilar artery (BA; insonation depth: 16 ± 3mm). MAP, CVP, heart rate (HR, 1/min), $petCO_2$ (mmHg), body temperature (°C) and TCD-data were monitored continuously and arterial and central venous blood gas analyses were performed every 15 min. Following two control measurements of CBF and TCD-parameters, angiotensinamid (1.25 mg; injection period 1 min) was administered iv. Injection of microspheres for CBF-measurements and registration of TCD-BFV were started 2 min following administration of angiotensin. For statistical analysis, Pearson product-moment correlations were calculated between TCD- and CBF-data. Data for different conditions were subjected to analysis of variance and Friedman´s test for repeated measurements. Significance was assumed at $p<0.05$. Data are expressed as mean ± standard deviation (SD).

Results: Following administration of angiotensin MAP increased significantly from 105.1 ± 12.4 mmHg at control to 211.2 ± 33.5 mmHg ($p<0.001$), associated with a slight but insignificant increase in HR from 72.6±19.7 1/min (control) to 77.0±30.4 1/min during hypertension. Table 1 summarizes relative changes of two control measurements (controls = 100%) of rCBF, gCBF and TCD-data versus the period of extreme hypertension. Correlations between the relative increases in CBF and TCD are displayed in table 2. Absolute gCBF increased significantly from 0.79±0.36 ml/g/min at control to 1.27 ± 0.59 ml/g/min during hypertension. Absolute TCD-data: Baseline recordings: Vsyst = 21.7±8.9 cm/sec; Vmean = 15.3 ± 6.9 cm/sec. Hypertension: Vsyst = 28.5 ± 12.8 cm/sec; Vmean = 18.1±8.6 cm/sec. In contrast to relative changes, the correlation between absolute CBF-data and absolute TCD-parameters was poor. HR, CVP, body temperature and arterial and central venous blood gas data were not significantly different from control.

	CBFcortex		CBFbrainstem		gCBF		Vsyst		Vmean	
1	101 ± 9		103 ± 31		102 ± 21		100 ± 5		98 ± 8	
2	99 ± 9		97 ± 28		99 ± 16		102 ± 4		102 ± 9	
3	188 ± 88	*	138 ± 64	*	170 ± 71	*	120 ± 32	*	118 ± 39	*

Table 1: Percentage changes (mean ± SD) of cortical (CBFcortex), brainstem (CBFbrainstem) and global cerebral blood flow (gCBF) versus systolic (Vsyst) and mean blood flow velocities (Vmean) during control (100 %=mean of 1 and 2) in comparison to angiotensin-induced arterial hypertension (line 3) in 10 dogs. (* = significant vs. controls; $p<0.05$)

	CBFcortex		CBFbrainstem		gCBF	
Vsyst	0.81	***	0.49	*	0.77	***
Vmean	0.68	***	0.34	*	0.58	**

Table 2: Correlation of %-changes between cortical (CBFcortex), brainstem (CBFbrainstem) and global cerebral blood flow (gCBF) versus systolic (Vsyst) and mean blood flow velocities (Vmean) during control versus angiotensin-induced arterial hypertension in 10 dogs. (*=$p<0.05$; **=$p<0.01$; ***=$p<0.001$)

Discussion: Angiotensin has been employed for the investigation of cerebral hemodynamic responses during systemic arterial hypertension exerting only minor or no cerebral vascular constricting effects or impairment of autoregulation (5). Our results with increases in gCBF and rCBF during excessive arterial hypertension suggest a pressure-dependent cerebral perfusion beyond the upper limit of cerebral autoregulation. The relative increases in CBF were more pronounced than the increases in BFV. This may confirm the assumption of impaired autoregulation and may represent the effect of hypertension-induced distending transmural pressure with consecutive dilatation of the insonated vessel segment and a nonlinear response of BFV in comparison to CBF. The acceptable correlations between concomitant CBF- and BFV-increases indicate that relative changes of CBF following angiotensin-induced extreme hypertension can be assessed by TCD and that this method may serve as a noninvasive and continuous monitoring system of relative changes in CBF in situations of compromised cerebral autoregulation during general anesthesia. In the light of our results TCD-monitoring has clinical implications due to potential hazards induced by cerebral perfusion beyond the upper limit of autoregulation. However, the individual relative increase in cerebral BFV indicating detrimental increases in cerebral perfusion still has to be defined. In addition, our results demonstrate that TCD-data do not provide any information about absolute CBF-values as indicated by a poor correlation. For the first time our data demonstrate an acceptable correlation between relative changes in TCD-BFV and CBF during arterial hypertension in dogs.

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Title: THE PHARMACOKINETICS OF VECURONIUM DURING LIVER TRANSPLANTATION IN HUMANS.

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Introduction. Studies in humans and cats suggest that vecuronium is rapidly taken up in the liver, following intravenous injection.[1,2] Exclusion of the liver from the circulation should therefore have significant effects on vecuronium distribution and clearance. To test this hypothesis, we studied the pharmacokinetics of vecuronium in patients during two different phases of orthotopic liver transplantation.

Methods. Following approval by our Committee for Human Research, 7 patients, ASA class III, scheduled for orthotopic liver transplantation gave written informed consent. No patient received premedication and anesthesia was induced with sodium pentothal, 3 to 5 mg/kg iv. Succinylcholine, 1.5 mg/kg iv, was used to facilitate tracheal intubation. Anesthesia was maintained with isoflurane, 0.4-1.0%, in an air/oxygen mixture. Narcotics (fentanyl and/or morphine) and midazolam were administered as clinically indicated. Vital signs were monitored and maintained according to appropriate clinical standards for the surgical procedure. Prior to skin incision, the first dose of vecuronium, 0.1 mg/kg, was administered as an intravenous infusion over 1 minute. Arterial blood samples were drawn at -5, 1, 3, 5, 7, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes thereafter, or until the dissection phase of the surgery was completed. At the start of the anhepatic period, which lasts between 30 and 40 min, a second infusion of vecuronium, 0.1 mg/kg, was administered and blood samples were collected for the next 240 min at the above-listed time intervals. Samples were collected in heparinized silicone tubes, placed on ice, centrifuged within one hour, then acidified and stored at -20 °C until analysis. Plasma concentrations of vecuronium were measured by a sensitive and specific capillary gas chromatographic assay using nitrogen sensitive detection.[3] Concentration *vs.* time data were fit to both two- and three-compartment models by derivative-free, nonlinear regression. Pharmacokinetic variables derived for doses 1 and 2 were compared by Mann-Whitney U test, and differences were considered significant at $P < 0.05$.

Results. A three-compartment pharmacokinetic model provided the best fit of all plasma concentration *vs.* time curves. The values for total plasma clearance, volume of the second compartment and clearance from central to second compartment (clearance 1-2), were less following the second dose (anhepatic phase) than following the initial dose (Table 1).

Table 1.

Pharmacokinetic Variables for Vecuronium.

PHARMACOKINETIC VARIABLE	DOSE 1 n = 5	DOSE 2 n = 6
Volume of Central Compartment (ml/kg)	52±26	25±7
Volume of second compartment (ml/kg)	109±110*	37±7*
Clearance 1-2 (ml/kg/min)	8.2±5.8*	5.9±1.2*
Plasma Clearance (ml/kg/min)	3.4±0.6*	2.8±0.3*
Steady State Volume of Distribution (ml/kg)	313±143	229±90
Mean Residence Time (min)	90±31	83±33
Elimination half-life (min)	99±31	88±23

* $P < 0.05$ Dose 1 *vs* . Dose 2

Discussion. The decrease in the volume of the second compartment and in the clearance from the central to the second compartment during the anhepatic phase suggests that the liver is part of a peripheral compartment into which vecuronium rapidly distributes. This would be consistent with the findings of Bencini *et al.*[1,2] However, these variables are highly model-dependent and the differences could simply be a function of the modelling technique. The lower value of plasma clearance following dose 2 is due to the greater area under the plasma concentration *vs.* time curve. This may be a result of diminished vecuronium uptake into the liver during the anhepatic phase, or a consequence of reduced cardiac output secondary to reduced venous return following clamping of the vena cava. (Veno-venous bypass is not used.) We conclude that exclusion of the liver from the circulation has significant effects on vecuronium pharmacokinetics, and consider that this may be explained by either diminished hepatic uptake or decreased cardiac output.

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Title: MALIGNANT HYPERTHERMIA INDUCTION IN SUSCEPTIBLE SWINE FOLLOWING EXPOSURE TO ARDUAN

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Introduction: The neuromuscular blocking action of Arduan [pipecurium bromide, a2B, 16B-bis-(4'-dimethyl-1'-piperazino)-3a, 17B-diacetoxy-5-androstane-dibromide] infusion for one hour in seven MHS pigs and eight control pigs clearly demonstrates that Arduan did not have any significant effect on 32 measured and calculated parameters in control pigs and on 26 of the same parameters in MHS pigs.

Methods: ACUC #AR 86148 was approved for these animal experiments. Seven MHS pigs (wt 35.87Kg) and eight control pigs (wt 36.49Kg) were used. Thiopental (22mg/Kg) was given for sedation. The animal was intubated and mechanicaly ventilated. Surgical cutdowns were completed to the external jugular vein and carotid artery. An Opticath catheter was threaded to the wedge position in the pulmonary artery. A Millar Mikro-Tip pressure transducer catheter was retrograde threaded to the left ventricle. End tidal CO_2 was monitored with the Cavitron-Anarad Gas Analyzer. A Grass FT10 transducer, HSE neuromuscular monitor, and HSE neurostimulator set at supramaximal (TO4) (0.2ms,2Hz,15sec) was used to stimulate the left peroneal nerve and record the twitch response. The 34 measured and calculated parameters were cardiac output, right ventricular stroke work index, coronary perfusion pressure, rate pressure product, arterial pH, arterial pCO_2, arterial bicarbonate, arterial O_2% saturation, arterial pO_2, arterial base excess, venous pH, venous bicarbonate, venous pCO_2, venous O_2% saturation, venous pO_2, venous lactate, venous base excess, central venous pressure, mean pulmonary artery pressure, pulmonary vascular resistance, pulmonary capillary wedge pressure, end tidal CO_2, core temperature, rectal temperature, mean arterial pressure, total peripheral resistance, heart rate, cardiac index, stroke volume, stroke volume index, left ventricular stroke work index, left ventricular contractility (dP/dT), hemoglobin, and hematocrit and muscle twitch response.

Results: Arduan had a significant effect on two measured parameters in control pigs. They were: venous % saturation increased from 75.13 % up to 78.72 % with a ($P<9.8^{-3}$); and venous pO2 increased from 41.19 Torr up to 44.67 Torr with a ($P<0.001$). The significant effect of Arduan infusion for one hour in MHS pigs was on venous HCO_3 (decrease from 27.76 down to 24.57 mEq/L with a ($P<3.7^{-3}$); venous base excess (decrease from 2.44 down to -0.23 mM/L with a ($P<0.005$); core temperature (decrease from 37.54 down to 37.14°C) with a ($P<0.018$); rectal temperature (decrease from 37.74 down to 37.27°C) with a ($P<0.0047$); venous % saturation from 68.23 % up to 75.16 % with a ($P<0.001$); venous pCO_2 decreased from 47.09 Torr to 43.02 Torr with a ($P<0.04$); venous pO_2 increased from 37.00 Torr up to 41.63 Torr with a ($P<4.0^{-5}$); and venous lactate decreased from 1.01 mM/L down to 0.68 mM/L with a ($P<0.01$).

Discussion: The eight significant effects of Arduan on MHS pigs were beneficial i.e., they decreased metabolic rate and body temperature and thereby decreased the heat load in the MHS pigs. This data strongly suggests that the heat production in MHS pigs is mediated through a neural mechanism. Blockade of the myoneural junction with Arduan shuts down the neurogenically mediated heat production in muscle tissues. This data confirms, from a different experimental viewpoint, our previous observation that total myoneural blockade with Metubine Iodide (6) was capable of blocking the development of MH in MHS pigs. Arduan can decrease the rate of heat production in muscle tissue, thereby leading to decreased venous bicarbonate and decreased body temperature. Dose response testing demonstrated that Arduan has a rapid onset (67.5 ± 13.89 sec), was effective in the 60-90 ug/kg dose range, and had a duration 90 of 10.50 ± 3 minutes. Recovery from Arduan was rapid and required 4.36 ± 2.77 minutes for 25-75% recovery. Respiratory acidosis gave a 3.25% increase and respiratory alkalosis gave a 1.80% increase which had minimal effect on the neuromuscular blocking activity of Arduan. The infusion dose required to maintain neuromuscular blockade in control pigs was 5.35 ug/kg/min. The onset time in MHS pigs was 72.86 ± 21.96 sec. with a duration 90 of 8.93 ± 2.81 min. The 25-75% recovery time was 4.79 ± 1.98 min. with a 2.4% decrease in twitch during respiratory acidosis and a 4.19% decrease in twitch during respiratory alkalosis in MHS pigs. The infusion dose required to maintain 95% neuromuscular blockade was 5.94 ug/kg/min in MHS pigs. The 100% blocking dose of Arduan in control pigs was 65.418 ug/kg. This dose was similar to the 100% blocking dose reported (as 59 ug/kg) used in human patients (1-3). The MHS pigs required an 77.446 ug/kg dose to produce a 100% neuromuscular blockade. The precise reason why MHS pigs required 118.38% more Arduan to produce the same degree of neuromuscular blockade was not apparent from our data set.

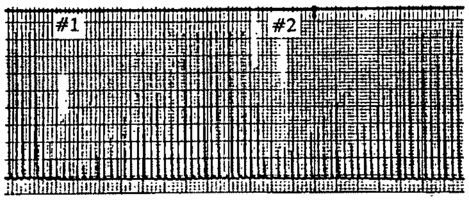

Fig 1: Supramaximal twitch record for pig #9-2 (BW 37.3 Kg) with paper speed at 5mm/min. Dose response #1 to 69.70 ug/Kg Arduan and #2 to 80.42 ug/Kg Arduan given ten minutes apart.

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Acknowledgement: Supported in part by Anesthesia Associates of Kansas City, MO for the MH pig colony, Biodynamics, Inc., East Millstone, NJ via Project #86-3079, and Oximetrix, Inc., Mountain View, CA for the Oximetrix Shaw Opticath^R recorders.

Title: ELEVATED CARDIAC OUTPUT AND BODY TEMPERATURES IN MAN HAVE NO EFFECT ON LIDOCAINE CLEARANCE

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Introduction: General hyperthermia is a frequently utilized addition to the therapeutic armamentarium for the treatment of malignancies. Drugs with antineoplastic properties are infused during this therapy and include the local anesthetic lidocaine. Efficacious drug levels are achieved only at high plasma concentrations (6 mcg/ml). Clinically, no consideration has been given to the potential consequences of physiological changes induced by hyperthermia upon lidocaine's disposition. It is established that lidocaine's elimination is dependent upon cardiac output and that general hyperthermia is associated with an increase in cardiac output (1). We hypothesized that hyperthermia via the effect upon cardiac output alters the plasma concentration of lidocaine.

Methods: After receiving written informed consent, twelve (following approval of this project by the IRB of the University), fasting patients were taken to the operating room following premedication with lorazepam (3-4 mg), ninety minutes prior to arrival. Anesthetic induction consisted of sodium thiopental 3-5 mg/kg and pancuronium 0.1 mg/kg. Maintenance of the anesthetic consisted of nitrous oxide 70-80% in oxygen, fentanyl 3 mcg/kg as a bolus followed by 1 mcg/kg dosages every thirty to forty-five minutes. Catheters were placed in the radial and pulmonary arteries and a large bore venous catheter placed in the dorsum of the hand. Thermodilution cardiac outputs were recorded every thirty minutes along with both mixed venous and arterial blood gases (both corrected for temperature). The patient was then warmed to 41.5°C and maintained between 41.5° and 42° for the two hour duration of therapy. Following placement of the catheters the patient was given a bolus of lidocaine (100-200 mg) intravenously followed by an infusion of 2-4 mg per minute. Blood samples are drawn at minutes 1, 2, 4, 8, 16, and 30 following the initial dose of lidocaine and then at thirty minute intervals until the termination of treatment. Total duration of therapy was generally five to six hours. The determinations of lidocaine, MEGX and GX (the first and second metabolites of lidocaine) were performed according to a previously published method (2). Statistics - Plots of serum blood levels versus temperature, temperature versus time and serum lidocaine versus MEGX concentrations were all subjected to regression analysis and $P < .05$ considered significant. Cardiac outputs, whole body oxygen consumptions, and lidocaine clearance rates were averaged over two temperature ranges (36.6-37.8° for normothermia and 40-42°C for hyperthermia) and the results compared by t-test (one way for cardiac outputs and whole body oxygen consumption and two way for clearance rates). Curves were fitted using curvilinear least squares second order regression equations.

Results: Total dose of lidocaine for the duration of the therapy as well as the remainder of the demographic criteria are given in Table 1. Figure 1 displays the plot of serum lidocaine concentrations against temperature. Clearance of lidocaine likewise remained unaffected throughout the duration of the treatment (Table 1). This was despite marked increases in both cardiac output and whole body oxygen consumption. Figure 2 demonstrates the rate of rise of temperatures throughout the duration of lidocaine therapy for the group. There are no statistically significant differences in either serum levels or clearance rates for lidocaine despite significant changes in both cardiac output and oxygen consumption.

Discussion: We were fortunate to have a human model of hyperthermia. This study addresses the effect that hyperthermia has upon cardiac physiology and the subsequent effect upon the disposition of a rapidly cleared drug like lidocaine. Lidocaine has a high (0.7-0.9) extraction ratio and is sensitive to changes in hepatic blood flow. A number of other factors besides temperature and cardiac output effect liver blood flow (anesthetics, method of ventilation, oxygenation, carbon dioxide concentrations and position) however, none of these were altered during the course of therapy. Serum catecholamines also effect liver blood flow and rise during the course of hyperthermic therapy (3). We are presently engaged in work to delineate alterations in hepatic blood flow during hyperthermia. Although elevated cardiac outputs and hyperthermia have no effect upon clearance rates of lidocaine we cannot make the same assumption about liver blood flow.

TABLE 1

	WT.	TOTAL DOSE	DURATION	CLEARANCE	C.O.	VO_2
N	-	-	-	1542	7.78	101
				(587)	(1.44)	(12.7)
H	75	1176	339	1487	*12.98	*145
	(15)	(400)		(507)	(1.86)	(18.3)
	kg	mg	min	ml/min	L/min	ml/min

N=Normothermic; H=Hyperthermic. All values are mean ± standard deviation *p .05

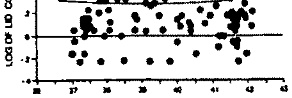

FIGURE 1

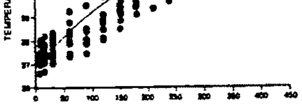

FIGURE 2

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Title: MYOCARDIAL INTERSTITIAL CHANGES IN HUMANS WITH CONGESTIVE CARDIOMYOPATHY

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Introduction: We have previously documented that the rate of formation and elimination of myocardial edema fluid is important in determining global left ventricular function. Experimental models of cardiac failure which elevate right atrial pressure result in large increases in myocardial edema (1). With the development of myocardial edema the interstitial matrix undergoes changes which result in the deposition of collagen (1). We hypothesized that the hearts of potential transplant patients with chronic biventricular failure should undergo interstitial changes in collagen content secondary to chronic myocardial edema. To examine these changes we assessed collagen content by hydroxyproline assay in ten samples of noninfarcted human myocardium removed at the time of transplantation.

Methods: All hearts selected for analysis were from patients with signs and symptoms of severe biventricular failure. All hearts were removed soon after the onset of cardiopulmonary bypass but none received cardioplegia. Two small, approximately 5 gram pieces of noninfarcted left ventricular myocardium were removed and placed into iced test tubes. These tubes were then immersed in iced saline and frozen (-15 to -10°C) until later analysis for hydroxyproline content. Collagen is approximately 13.4% hydroxyproline by weight thus all hydroxyproline results were multiplied by a constant factor of 7.46 to estimate final collagen content. Analysis of hydroxyproline content was carried out following acid hydrolysis and oxidation to a pyrrole (2). In addition one sample was taken from an area of infarct for comparison of collagen content.

Results: The average collagen content in myocardium samples from patients with congestive cardiomyopathy was 4.8 ± 1.5 mg per 100 mg of dry weight [vs. control value of 2.9 ± 0.24 mg (2)]. In contrast infarcted ventricle collagen content was 13.03 mg per 100 mg of dry weight.

Discussion: Our data provides original evidence supporting the role of myocardial edema in interstitial alterations following the onset of biventricular failure in humans. Thus the increase in collagen content in noninfarcted left ventricular myocardium was less than in the infarcted zone. (used as a reference for an increase in collagen in fibrotic processes).

We previously demonstrated a correlation between myocardial edema and decrease in cardiac function (1). Therefore our data also supports the concept 1) that the myocardial depression associated with cardiac failure is at least in part due to edema and 2) that consideration should be given to the treatment of myocardial edema in patients with cardiac failure. One approach being therapy directed to decreasing right atrial pressure. High right atrial pressures directly inhibit the elimination of myocardial edema by elevating superior venal caval pressure and promotes the formation of edema by elevating coronary sinus pressure (3).

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TITLE: A COMPARISON OF FIRST AND SUBSEQUENT EPIDURALS WITH RESPECT TO PERFORMANCE AND EFFICACY

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AFFILIATION: Departments of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal, Quebec, Canada.

INTRODUCTION:

Epidural analgesia is provided for 65% of primipara in our institution. The impact of previous epidurals on the performance and outcome of subsequent epidurals has not been studied in parturients. An increased incidence of epidural failure with increasing number of epidurals has been demonstrated during lithotripsy (1). Fibrous bands have been demonstrated post-mortem in the epidural space (2). It is interesting to speculate whether epidural insertion may lead to the formation of adhesions within the space.

The aim of this cross-sectional study was to compare first epidurals with subsequent epidurals with respect to problems at insertion and to outcome The results of the first 111 patients are presented.

METHODS:

With Ethics Committee approval a standard form was designed to record the patient's demographic data and details of epidural performance and outcome. Prior to epidural insertion the patient was asked to assess her pain on a standard 10 cm linear analogue scale (LAS). A standard procedure was followed for epidural insertion and establishment of block : sitting position, mid-line approach, loss of resistance to air, 0.25% bupivacaine given as three 4 cc increments, through the needle and on right and left sides. During catheter insertion the patient was requested to report any pain or paresthesia experienced. The operator recorded the occurrence of paresthesia, difficult catheter insertion, blood in the catheter or needle and CSF tap on the form.

Thirty minutes after insertion of the epidural the patient completed a second LAS and the level of blockade was defined by ability to distinguish cold. Top-ups and interval from epidural insertion to delivery were recorded. Efficacy of any previous epidural was noted (Group 2).

RESULTS:

Seventy-four first epidurals (Group 1) and 37 second or third epidurals (Group 2) were performed. The 2 groups were comparable in terms of age, weight and height. Mean cervical dilatation was not significantly different between the groups (3.1 vs 3.7 cm). There were primipara and multipara in Group 1. Group 2 were all multipara. Mean duration of labor was 6.75 hours in Group 1 (range 1.2 - 24.33 hrs) and 3.75 hrs in Group 2 (range 1.2-14.66 hrs).

The incidence of problems at insertion and of unilateral block as assessed at 30 mins are shown in Table 1. There were no dural taps. One patient in Group 1 had a missed segment.

One patient had had previous unilateral block, all other Group 2 patients had successful epidurals previously.

TABLE 1

Percentage incidence of events at insertion and unilateral block at 3 minutes.

	Blood	Paresthesia	Catheter difficulty	Unilateral block
Group 1	10.8	17.6	12.2	8.1
Group 2	16.2	24.3	21.6	18.9

There was no significant difference between the groups on chi-squared testing although there was a trend apparent for unilateral block ($p = 0.0898$).

DISCUSSION:

This comparison of first and subsequent epidurals sought to eliminate the problem of differences in duration of labor by assessing epidural efficacy at 30 minutes post-insertion. At this time there was a 2-fold greater incidence of unilateral block in Group 2 (NS).

Three patients in Group 1 had non-resolution of unilateral block with top-up or catheter manipulation, 1 requiring repeat epidural; 3 in Group 2 did not resolve, 1 was repeated. There was thus a two-fold greater incidence of continuing inadequate block in Group 2 although this did not reach statistical significance.

Combining the 2 groups, problems at insertion tended to cluster. Of 17 cases with difficult catheter insertion 11 had either paresthesia or blood in the catheter; of 14 patients with blood in the catheter 7 had paresthesia or catheter insertion difficulty. However these events were only associated with unilateral block in 4 of 12 cases.

These preliminary results suggest an increased rate of unilateral block in repeat epidurals. The causes of this are unclear. Previous cannulation of the epidural space is the obvious difference between the two groups. However, dwelling time of an epidural catheter is unlikely to be sufficient to cause a tissue reaction with adhesion formation.

This study also provides evidence of effective epidural block in the majority of multiparous patients despite shorter duration of labor.

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TITLE: ORG 9426, A NEW SHORT-ACTING MUSCLE RELAXANT: ONSET AND DURATION OF ACTION

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Introduction:

ORG 9426 is a short acting non depolarizing muscle relaxant which is similar to vecuronium. Animal studies have shown a shorter time of onset, duration of action, and recovery time than vecuronium. We are engaged in a study to determine this drug's onset and recovery time following single and multiple doses in humans.

Methods:

Eight ASA Class I-II patients (3 male: 5 female, mean age 45.2 yrs) scheduled for elective surgery were studied. These were compared with 6 selected patients of 35 who had received pipecuronium bromide. The study was reviewed and approved by the Thomas Jefferson University Hospital Institutional Review Board. Informed consent was obtained from all subjects.

Patients receiving ORG 9426 were premedicated with diazepam 100-150 mcg/kg p.o. 1 hour prior to surgery. Anesthetic induction and intubation were performed with sodium thiopental 4-8 mg/kg, fentanyl citrate 4-8 mcg/kg, 60% nitrous oxide, and enflurane 1-4%. After stable end tidal concentration (1-2%) of enflurane was established by infrared gas analysis (Datex), muscle relaxant was given. Neuromuscular function was monitored with a Digistim II peripheral nerve stimulator via surface electrodes placed over the ulnar nerve at the wrist. Repeat train of four stimuli, each of 2 Hz 0.2 msec duration, were delivered every 12 seconds. An F10 force transducer and Gould polygraph were used to collect the neuromuscular function data. The initial dose of relaxant (120-240 mcg/kg) was administered and effect monitored until maximal twitch depression occurred. At this point another dose of relaxant was given to a total of 300 mcg/kg. Anesthesia was maintained with 60% nitrous oxide, 0.5 - 1.2% enflurane, and 0.002 - 0.005 mg/kg/hr of fentanyl citrate. Additional doses (75-100 mcg/kg) of muscle relaxant were given as clinically indicated. Reversal of relaxant was performed with neostigmine 0.04 mg/kg and atropine 0.015 mg/kg.

Data for onset of blockade were analyzed for those patients whose block was at least 90% but less than 100%. These were compared with previously unpublished data of onset of pipecuronium bromide under balanced anesthesia using the same equipment and stimulation pattern. Six ASA Class I-II patients (all female, mean age 45.8 yrs) achieving similar level of blockade following pipecuronium were selected. Recovery time of twitch ratio from 10-25% was determined for all ORG 9426 doses given. Five patients who received multiple doses were analyzed for changes in recovery time with repeated doses. Clinical duration of blockade (drug administration to 25% recovery) was also calculated. Time to 10, 25, 50, 75, 90% and complete blockade for ORG 9426 and pipecuronium were compared by analysis of variance for repeated measures, as were recovery times; p<.05 was considered significant.

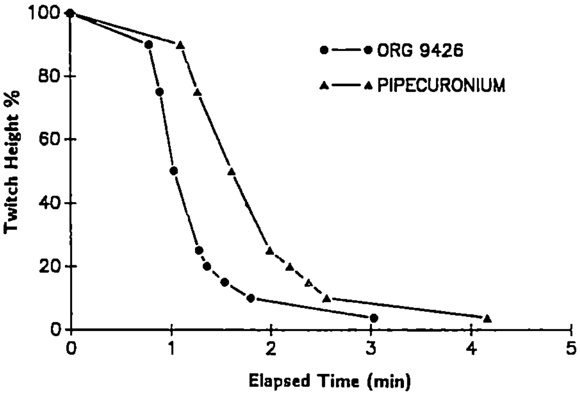

Figure 1 Time to onset of blockade for ORG 9426 and pipecuronium

Results:

The time to onset of ORG 9426 was more rapid than pipecuronium at all points studied (p<.05). Patients receiving ORG 9426 achieved 96% blockade by 3.03 ± 0.91 mins. as compared with 96.5% blockade in 4.16 ± 1.25 mins. for pipecuronium. This was significantly faster (p<.05) (Fig 1). Recovery from 10-25% of T1 ratio averaged 5.92 ± 1.25 mins. (mean of all doses given). The recovery time after the initial dose was significantly (p<.05) shorter than other times but subsequent recovery times did not differ (Table 1). There appeared to be little to no cumulation of the drug following repeated doses. (Table 1) The clinical duration from drug dosage to 25% T1 recovery following the initial dose of 300 mcg/kg was 24.12 ± 7.15 mins. Mean T1 blockade was 98.6% at this dosage.

Discussion:

ORG 9426 is a steroidal muscle relaxant with a rapid onset and short duration of activity. This rapid onset is consistent with its low potency. Recent studies have suggested that speed of onset is inversely related to potency (1,2). The dosage of pipecuronium given was 35% of that of ORG 9426 and its onset was significantly slower. This suggests a more rapid onset of ORG 9426 compared to more potent blockers. The short duration of this drug is another valuable feature. Further studies are necessary to clarify the role of this interesting compound.

Table 1 Time for 10-25% T1 recovery after repeated doses of ORG 9426

Dose	1	2	3	4	5	6
No Pts.	5	5	5	4	4	3
Time	4.7	6.1	7.1	6.1	6.2	5.9
S.D.	±0.7	±0.9.	±1.9	±1.0	±0.3	±1.0

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This study supported in part by Organon, Inc; AKZO Pharma Division.

Title: TRACHEAL TUBE INTRALUMINAL FLAME SPREAD IN OPPOSED FLOW OXIDANT: HELIUM VERSUS NITROGEN DILUTION.

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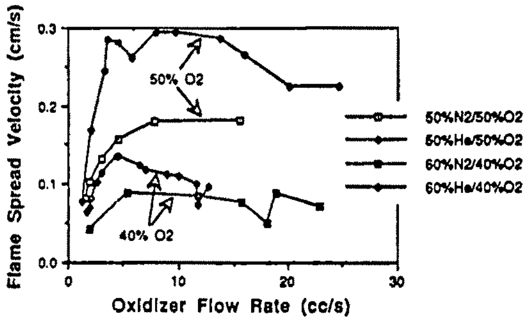
Introduction. Tracheal tube fires continue to present a hazard to patients during laser surgery. Since helium dilution of oxygen is used in an attempt to decrease ignition susceptibility,[1] we compared the effect of helium and nitrogen dilution on the flame spread velocity along the inner surface of polyvinylchloride (PVC) tracheal tubes, should ignition occur. The flame spread velocity is defined as the rate at which a flame front advances over the surface of a fuel against the direction of the oxidizer flow.

Methods. Polyvinylchloride tubes of 5.5 mm inner diameter, 7 cm long and marked at their midsections into 4 cm lengths, were slipped over the end of a stainless steel tube with an outer diameter of 6.0 mm. The stainless steel tube was horizontally positioned and the PVC tube was otherwise unsupported.

Oxygen, helium, and nitrogen were obtained from compressed gas cylinders. Pressures were reduced to 50 psi by variable pressure regulators. Flow was controlled by needle valve flowmeters and confirmed by a bubble flowmeter. Forty and fifty percent oxygen in either nitrogen or helium dilution entered the stainless steel tube.

The free end of the PVC tube was ignited by a butene torch in ambient air and the intraluminal flame was observed as it spread against the oxidant flow. Time of spread for a 4 cm length was determined by stopwatch, and flame spread velocity was determined for various flow rates.

Results. The figure below shows a comparison of the flame spread velocity as a function of the oxidizer flow rate.



After an initial increase, the flame spread velocity reaches a fairly constant value. Comparison of the diluents reveals a flame spread velocity in helium dilution to be greater than that for nitrogen dilution at comparable oxidant flow rates.

With decreasing oxidizer flow, the flame spread velocity begins to fall at approximately the same flow for all oxidizers. Below a certain flow, the tube cannot be ignited.

Discussion. The implications of extinction at low flow rates is that flame spread in horizontally positioned tubes cannot occur without flow. Therefore convection, whether natural or forced, may be necessary for some solids to burn in stagnant environments. Clinically, these results suggest that if the laser is pulsed only during the exhalation pause, the tube may not ignite. This hypothesis is presently being tested in our laboratory.

The fact that horizontally positioned tubes do not ignite at low flow may be related to the mixing of ambient air with the oxidant flow. However, when the oxidizer flow is abruptly shut off, the flame extinguishes and does not continue to propagate even when the oxidizer is 100% oxygen. Further, this possible ambient air effect does not influence the decrease in flame spread velocity with decreasing oxidizer flow since, in the presence of an established flame, the ambient air is separated from the oxidizer by the flame.

The 40% oxygen in helium dilution curve is unique in that an "upper flammability limit" is observed. The tube does not ignite for flow rates greater than shown. It is anticipated that the same phenomenon would be observed for other oxidizers at higher flow rates than measured, or for lower oxygen concentrations in nitrogen dilution.[2]

Since helium has a higher diffusion coefficient than nitrogen, it promotes the diffusion of heat away from a heated fuel thereby inhibiting its ignition. Once ignited, however, the concentration of oxygen necessary to maintain a candle-like flame on a tracheal tube is not clinically significantly different in nitrogen or helium dilution.[3]

The intraluminal flame spread velocity is greater for PVC tubes exposed to oxygen in helium dilution than when exposed to the same percentage of oxygen in nitrogen dilution at comparable flows because of helium's higher diffusion coefficient and lower specific heat, hence higher flame temperature. This additional potential danger of helium dilution for laser surgery of the airway must be considered.

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TITLE : COMPARISON OF CHANGES IN ULTRASONIC FLOW PROBE, ESOPHAGEAL DOPPLER AND THERMODILUTION CARDIAC OUTPUT AFTER CHANGES IN PRELOAD, AFTERLOAD, AND CONTRACTILITY IN PIGS

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INTRODUCTION: Esophageal Doppler (Dopp) can measure aortic blood velocity which, when integrated and multiplied times the cross sectional area of the aorta and multiplied times heart rate yields cardiac output (CO). The agreement of Dopp CO with thermodilution (TD) CO has been reported to be variable (1,2). These studies however, did not evaluate one possible use of continuous Dopp CO measurement: the ability to detect trend changes in CO.

The purpose of this study was to compare how well changes in TD and Dopp CO measurement agree with changes in CO measured by a reference CO measurement method, the ultrasonic flow probe (FP) (3).

METHODS: This work was approved by the Animal Research Committee. Six Duroc pigs were anesthetized with halothane, N_2O, and O_2. Femoral artery catheters were inserted via the femoral vein. TD CO was measured using 5cc of iced D_5W. FP CO was measured with a calibrated 16mm ultrasonic flow probe (Transonics 101D, Ithaca, NY) introduced through a median sternotomy incision and placed around the ascending aortic root. Dopp CO was measured with a continuous wave Doppler probe inserted in the esophagus (L3000, Lawrence Medical Systems, Camarillo, CA).

We independently titrated drug infusion, halothane, hemorrhage, PEEP, or IVC compression to increase or decrease preload (groups 1 & 2), increase or decrease afterload (groups 3 & 4), or increase or decrease contractility (groups 5 & 6) until the FP CO changed > 10%. We simultaneously measured TD, Dopp, and FP CO in triplicate before and after each intervention. The % change in TD, Dopp, and FP CO was calculated for each intervention. We considered FP measurement as the reference and defined that TD and Dopp agreed with FP when their CO changed >10% in the same direction as the FP CO.

We used paired t-test to compare the % Δ CO and the difference in CO change between the groups.

RESULTS: The results are summarized in Tables 1 & 2. Of 95 measurement sets, FP CO changed > 10% 90 times. TD agreed with FP 72 times, disagreed 3 times, changed < 10% 15 times, and had a 80% sensitivity in detecting a 10% change in FP CO. Dopp agreed with FP 59 times, disagreed 6 times, changed < 10% 25 times, and had a 62% sensitivity in detecting a 10% change in FP CO.

There was no significant difference between changes in FP CO and TD CO in any group. In contrast, changes in Dopp CO and FP CO were different for all afterload and contractility groups.

DISCUSSION: FP CO was chosen as the reference measurement because, unlike TD CO, FP CO measures stroke volume on a beat by beat basis and, unlike Dopp CO, can detect all the blood moving in the ascending aorta.

Dopp CO was generally less sensitive than TD CO to changes in FP CO except for decreased afterload. Changes in CO due to changes in preload were not significantly different between TD and Dopp. Some of the discrepancy between Dopp CO and the other two CO methods in groups 3-6 may be due to changes in the aortic diameter (1).

Changes in TD and Dopp CO > 10% reflected true directional changes in FP CO 96% and 91% of the time respectively. When Dopp CO is used as the sole CO monitor, it may not detect all changes in CO > 10%. However, when Dopp CO does change > 10%, CO has probably truly changed, particularly if the change in CO is due to a change in preload.

TABLE 1 CHANGES IN CARDIAC OUTPUT WITH THREE MEASUREMENT METHODS

	n	%Δ FP±sd	%Δ TD±sd	%Δ Dopp±sd	
Group 1	11	32.4±27.3	38.4±31.9	23.9±39.3	
Group 2	28	-38.5±20.4	-31.8±20.8	-26.0±23.1	*
Group 3	3	6.7±21.3	1.1±21.6	-30.8± 7.1	*
Group 4	12	8.0±28.9	19.8±26.6	50.1±41.7	**;#
Group 5	13	42.0±29.3	48.3±33.9	12.8±26.3	**;#
Group 6	19	-40.7±21.8	-38.4±16.0	-26.6±24.4	

*p < .05 between FP and Dopp; **p < .02 between FP and Dopp; # p < .05 between TD and Dopp; ## p < .02 between TD and Dopp.

TABLE 2 COMPARISON OF DIFFERENCES IN CARDIAC OUTPUT

	n	(ΔTD-ΔFP)±sd	(ΔDopp-ΔFP)±sd	p
Group 1	11	5.9±19.6	- 8.5±28.8	0.184
Group 2	28	6.7±17.3	12.5±14.3	0.179
Group 3	3	5.6± 0.5	37.5±14.3	0.018
Group 4	12	11.8±12.4	42.1±31.5	0.005
Group 5	13	6.2±30.1	-29.2±22.0	0.002
Group 6	19	2.3±17.8	14.1±10.7	0.019

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Title: DOSE FINDING STUDY OF MIDAZOLAM PREMEDICATION IN THE ELDERLY.

Authors: H.Y. Wong, M.D., R.J. Fragen, M.D., K.L. Dunn, R.N.
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INTRODUCTION. Midazolam is a popular benzodiazepine for preanesthetic medication (premed) and sedation. Reports of cardiorespiratory arrests after its use led to suggestions of reduced dosing in the elderly. This study is a randomized, double-blinded, placebo-controlled, dose-finding study of midazolam as intramuscular(i.m.) premed in older patients.

METHODS. After institutional approval and written informed consent, 100 elective surgical patients, aged 60 and above, of ASA Class I,II,or III, who expressed preoperative anxiety were enrolled. They were randomly assigned to receive a placebo, or 1 mg, 2 mg, or 3 mg of midazolam, each in 1 ml of amber-colored liquid. The medication was injected i.m. about one hour before the anticipated start of anesthesia. A blinded research nurse unobtrusively observed the patient for 60 minutes. No supplemental oxygen was used. Brachial artery blood pressure, heart rate and digital pulse oximetry were recorded half-hourly. The following items were assessed every fifteen minutes.

A) Drowsiness--- rated on a five-point scale by the research nurse: 0=Wide awake; 1= Awake but signs of drowsiness; 2= Asleep but responds to spoken word; 3= Asleep, unresponsive to spoken word, but responds to gentle shaking; 4= Asleep, unresponsive to verbal or tactile stimuli.

B) Anxiety-- rated by the patients on a 100 mm Visual Analog Scale, with the words 'No Anxiety' at one end and 'Extreme Anxiety' at the other.

C) Amnesia -- a different picture card was shown in random order to the patients at each assessment. On the following day, the patient's ability to select out of a composite picture each of the five pictures shown indicated presence or absence of amnesia for the corresponding period.

For the purpose of data analysis, patients were classified as non-responders (drowsiness score=0) or responders (drowsiness score= 1, 2, 3, or 4) at each assessment period. ANOVA and Non-parametric tests (Fisher Exact Test and Wilcoxon rank-sum test) were used to compare between treatment groups. Statistical significance was defined as $p<0.05$.

RESULTS. The 100 patients were about equally distributed among the 4 groups with no significant difference between groups in term of age, sex, weight, and ASA Status. The median ages for the placebo and the 3 midazolam groups were 72, 68, 69, and 68 years respectively. The range of weight for the whole group was 52-100 kg.

Drowsiness---Compared with placebo, all 3 doses of midazolam were associated with higher proportion of patients who were responders (drowsiness score=1-4). 3 mg dose was associated with more responders than 1 mg and 2 mg dose.

Three patients reached drowsiness level of 4. One received 3 mg and two received 2 mg of midazolam.

Anxiety---The 3 patients who reached drowsiness score of 4 ,and 5 patients who had baseline anxiety score <10 were omitted from the analysis of anxiety. Compared with placebo, all doses of midazolam were associated with decrease in anxiety level. This effect was significant at all observation points with the 2 mg and 3 mg doses; with the 1 mg dose, the decrease was significant only at 60 minutes.

Recall--- Compared with placebo, all doses of midazolam were associated with impairment in recall. Significance was seen only at 15 and 30 minutes with the 1 mg dose; with the 2 mg and 3 mg doses, there was significant difference at all assessment points.

Vital Signs---There was no clinically significant change in blood pressure, heart rate, or SaO_2, although statistically significant decrease in blood pressure and SaO_2 was seen in all midazolam groups.

DISCUSSION. In this study of patients above 60 years of age, midazolam in the reduced doses of 1, 2 or 3 mg intramuscularly was efficacious as preanesthetic medication for producing sedative/hypnotic, anxiolytic, and amnesic effects. These desirable effects appeared more rapidly (15 minutes after injection) and remained more consistently throughout the 60 minutes period with the 2 mg and 3 mg doses. These doses are considerably lower than those previously recommended for the general population, i.e. 0.07-0.10 mg/kg[1]. Nevertheless, 3 patients attained what could be considered oversedated state (Drowsiness score=4, or asleep and unresponsive to verbal or tactile stimulation). The per kg dose for the 3 patients were 0.041 mg, 0.038 mg and 0.024 mg.

There were no clinically significant changes in blood pressure, heart rate, or arterial oxygen saturation, even in the 3 oversedated patients.

This study supports the general notion that when used in elderly patients, the dose of midazolam could be reduced to 2 to 3 mg for dependable onset and duration of desired effects.

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Title: SINGLE-DOSE EVALUATION OF A-4492 FOR ACUTE POST-OPERATIVE PAIN

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Introduction. A-4492(Pentamorphone), a morphinan derivative, is a powerful analgesic in both animals and humans. This study is a randomized, double-blinded, placebo-controlled dose-finding study to evaluate the efficacy of a single injection to provide postoperative analgesia.

Methods. After institutional approval and written informed consent, 44 ASA Class I or II patients, aged 18-60, undergoing major abdominal or orthopedic surgery were entered into the study and randomized to receive one of the following doses of A-4492: a)0.08 mg/kg, b)0.16 mg/kg, c)0.24 mg/kg or d) a placebo. Patients received intramuscular midazolam premedication and thiopental-nitrous oxide-isoflurane-muscle relaxant anesthesia. Upon awakening from anesthesia and complaint of pain by the patient, the following were assessed:
1) Pain intensity by the patient with Visual Analogue Scale (VAS) and Verbal Pain Scale (VPS): none, mild, moderate, severe, or excruciating. 2) Degree of sedation by a blinded investigator as: i)asleep and difficult to arouse, ii)asleep but easy to arouse, iii)awake but calm, and iv)awake but hyperactive. 3)Blood pressure, heart rate, respiratory rate and arterial oxygen saturation(SaO2). The assigned medication was then given intravenously by another investigator and the aforementioned assessments repeated at 5, 10, 15, 30, and 60 minutes. Pain relief was considered inadequate if after 10 minutes the pain verbal scale was severe or excruciating, and morphine sulfate in 2 mg increments would be given intravenously to relieve pain. The time interval before the 1st morphine dose and the total amount of morphine in the first 60 minutes were noted.

Demographic data, length of surgery, time to first dose of medication, and total amount of supplemental morphine in the first hour were analyzed with ANOVA. Within-group comparison of VAS, VPS, degree of sedation, and time to first supplemental morphine was by Friedman 2 way ANOVA. Between group comparison was by Kruskal Wallis and Mann-Whitney U Tests.
Statistical significance was defined as $p<0.05$.

Results.The 44 patients were equally distributed among the 4 groups. There was no difference between the groups in distribution of age, sex, height, weight, length of operation, and time between end of operation and administration of the test medication.

No significant difference was seen in pain intensity (expressed as VAS) within each group over time, or between groups at each assessment. However, the verbal pain scores of the 0.16 mg/kg and 0.24 mg/kg groups were different from the placebo group at 5 minutes. The degree of sedation showed no significant difference over time within each group, but at 5 minutes, the 0.24 mg/kg group was significantly more sedated than the placebo group.

The time interval before the first supplemental intravenous morphine was significantly longer in the 0.16 mg/kg and 0.24 mg/kg groups. However, the total amount of morphine required in the first hour was not different between groups. No clinically significant change was seen in heart rate, blood pressure or SaO2. In the 0.08 mg/kg group, the respiratory rate was significantly slower at 5 minutes, and in the 0.24 mg/kg group, at 10 minutes, when compared with baseline. These changes were not clinically significant.

Discussion.The doses of A-4492 studied in this acute pain model were not very effective in controlling postoperative pain. The small, but significant effect we saw with the two higher doses studied was short lasting. Because the side-effect profile was favorable with the 0.24 mg/kg dose, perhaps a higher dose of A-4492 should be studied for this degree of acute pain or A-4492 may be a very short acting analgesic in this dose range.

Title: **ANESTHESIOLOGISTS - THE PUBLIC'S PERCEPTION**

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Introduction: Historically the function of anesthesiologists has been poorly understood by the general public.[1] This has been attributed to both the public's lack of exposure to anesthesiologists and the failure of many anesthesiologists to adequately communicate with their patients prior to a procedure.[2] However in recent years, many anesthesiologists have branched out of the operating room to take more active (and visible) roles in intensive care units, acute and chronic pain services, and cardiac life support courses. Programs to educate patients about anesthesia by utilizing video tapes or booklets in addition to a thorough pre-operative interview have also been instituted by many anesthesia departments. In light of these efforts, this study was designed to contrast present public knowledge and opinion about the field of anesthesiology with that of nine other professions.

Methods: After Institutional Review Board approval, a survey consisting of 21 fill-in-the-blank questions was distributed to 125 people in an allergy clinic waiting room. The answers were selected from the following list of 10 professions:

a) Pediatrician (PEDI)
b) General Practitioner (GP)
c) Chiropractor (CHIRO)
d) General Surgeon (SURG)
e) Anesthesiologist (ANES)
f) Obstetrician (OB)
g) Cardiologist (CARD)
h) Emergency Room Dr.(ER)
i) Dentist (DENT)
j) Lawyer (LAW)

Each question requested 1,2,3, or "as many as applicable" answers. The participants nor the volunteer distributing the surveys knew the purpose of the survey. Surveys less than 2/3 complete were discarded. Statistical analysis utilized ANOVA and the single group Student's t-test.

Results: One hundred and sixteen surveys were tabulated. The surveys were divided into 4 groups: College graduates (N=32), High School graduates (N=47), Medical occupations (MO) (primarily nurses or support personnel) (N=19), and unknown level of education (N=18). Sixty percent of the participants were female. The mean age was 42 years old.

When asked "Which professional would you prefer to be?". The responses were: LAW-26%, PEDI-22% , GP-15%, OB-8%, ANES-7%, DENT-5%, CHIRO-5%, SURG-5%, CARD-4%, ER-3% (N=112). Of these choosing ANES, 38% (3/8) were in the MO group.

Thirty-one of 115 responders (27%) listed the ANES as a professional that is not required to be a physician. This was more responses than all the other medical professions combined ($p<0.02$) (Fig. 1).

When asked "Which professionals make the most amount of money for the least amount of work?", ANES were chosen more than twice as often as any other medical profession ($p<0.02$).

The people surveyed were requested to list the 3 professions that should be paid the most. ANES and GP were selected last among the medical professions (Fig. 2). Among the MO group ANES placed third behind CARD and ER.

When asked which physician is most qualified to manage the vital signs of a patient with heart disease in the operating room, the top choices were: ANES-48%, CARD-36%, SURG-9% (N=107).

Participants responded that ANES required the shortest duration of training of the medical professionals (7.7±0.4 years post high school, $p<0.05$ except for GP). Five percent of the participants felt that it required just 2 years of post high school training to become an ANES. Twenty four percent responded that the requirement was 4 years or less.

Excluding the MO group, 32% (31/97) ranked anesthesiology as one of the 3 most boring fields and 21% (24/113) thought it was one of the 3 most challenging. In the MO group the reverse occurred, more felt it would be challenging than boring - 39% (7/18) vs. 13% (2/15).

Fifty three percent (10/19) of the MO group choose anesthesiology as one of the three most stressful professions versus 23% (20/87) of the remaining participants.

Forty five percent (49/108) of responders listed ANES in the group of 3 professionals that choose their profession for its easy lifestyle.

Excluding the MO group, 48% (48/100) of respondents felt that an ANES was not qualified to supervise cardiac resuscitation (Fig. 3). Ninety-four percent (17/18) of the MO group knew that an ANES was qualified to supervise a cardiac resuscitation.

75% of participants picked the ANES as the professional with the most expertise in airway management (N=114).

Discussion: These results demonstrate the general public's continued lack of knowledge of the role of the ANES. Just over half of those surveyed knew that an ANES can supervise a cardiac resuscitation. Less than half choose the ANES as the most qualified to care for a cardiac patient in the operating room. One in four did not realize that an ANES is a physician. Compounding this lack of knowledge is the fact that the ANES typically leaves no tangible evidence of his efforts in the operating room.It is not surprising then that the general public perceives that the ANES is overpaid. One positive finding in this study was that the MO group had a higher regard for ANES than the general public did.This is probably related to their greater exposure to the field of anesthesiology. The authors believe that it is important to intensify efforts to educate patients and the general public about the anesthesiologist's role in the health care system.

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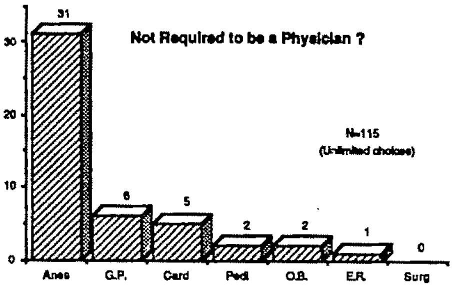

Fig. 1

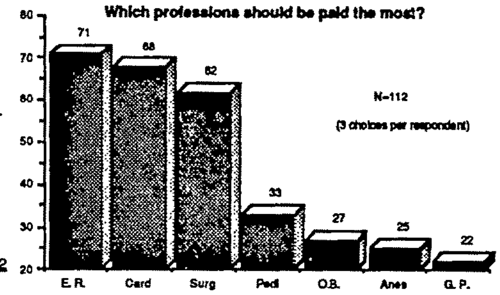

Fig. 2

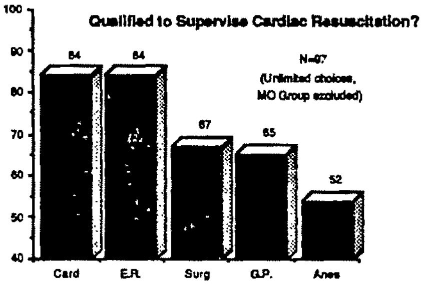

Fig. 3

Title: Evaluation Of The Fenem FEF End-Tidal CO2 Detector in a Dog Model of Cardiopulmonary Resuscitation

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Introduction

Outcome of cardiopulmonary resuscitation over the past 20 years is essentially unchanged. (1) The measurement of expired end-tidal carbon dioxide (ETCO2) during cardiopulmonary arrest assesses several variables: correct endotracheal tube placement, cardiac output, coronary perfusion pressure, adequacy of cardiac compressions, and restoration of spontaneous circulation. (2) ETCO2 has been clearly shown to be a prognostic indicator of successful resuscitation from cardiac arrest. (3) ETCO2 may provide the best overall assessment of the adequacy of mechanical and pharmacologic interventions during CPR by furnishing a breath-to-breath measure of metabolism, ventilation and circulation. Until recently, the technology for accurate monitoring of ETCO2 has been restricted to operating rooms and intensive care units. In October 1988 a small, portable, disposable device was introduced to assist in verifying proper placement of an endotracheal tube by a simple color change indicator. In this paper we evaluate the Fenem end-tidal CO2 detector device (FEF) (4) as a potential semiquantitative correlate of infrared capnography during actual CPR in a dog model.

Methods

Approval was obtained from the Institutional Animal Use Review Committee. Six healthy mongrel dogs were anesthetized with 20-40 mg/kg of pentobarbital, paralyzed with 0.1 mg/kg of pancuronium, intubated, and maintained with halothane 1.5% in 100% O2. Ventilator settings were standardized to weight, and rate was set at 10. A Transonics doppler flow probe was placed on the aorta and was calibrated against thermodilution cardiac outputs before each experiment. A Millar solid state pressure catheter was used for continuous monitoring of aortic root pressures. Subcutaneous electrodes were attached for ECG monitoring. An Ohmeda 5200 infrared capnography unit was calibrated before each experiment with high (5%) and low (0%) reference gases and sampled at the proximal end of the endotracheal tube. A Fenem End-tidal CO2 detector device (weight 1 oz, dead space 38 cc) was placed proximal to the IR uptake. Pressures, cardiac output, ECG, and ETCO2 were continuously recorded on a strip chart recorder.

The FEF circular color change indicator is divided into 3 color zones (A, B, C) comprised of 2 discrete shades each. Each color shade was assigned a number (1-6) for recording purposes during the experiment.

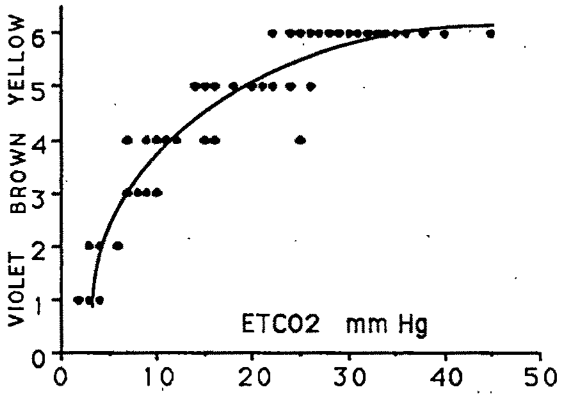
Animals were fibrillated and direct cardiac compressions @ 80-100 bpm were initiated at 1 min. All parameters were recorded at 3, 5, & 9 mins. Defibrillation was attempted in all dogs and successful in 5/6. Readings were made at 30 seconds, 1, 3, & 5 minutes following restoration of normal circulation. Fibrillation was again induced and ineffective compressions begun (mean arterial pressure < 40 mmHg and C.O. < 1.0 lpm), sodium bicarbonate (NaHCO3) 1 meq/kg was infused. FEF color and other parameters were recorded at 1, 3, & 5 mins. After all hemodynamic data was obtained, lidocaine (100 mg / 5cc), atropine (2 mg / 10cc), and epinephrine (1 mg / 10cc), were sequentially instilled into the endotracheal tube to assess the effect of this route of administration on the FEF.

One of us (REW), recorded all FEF colors while another (JH) recorded capnometry in an attempt to standardize and blind the experiments.

Results

During ineffective resuscitation ETCO2 averaged 6.7+/-1.4 and 8.4+/-4.7 at 3 and 5 minutes after administration of 1 mEq/kg NaHCO3. FEF registered in "B" (brown) range during this time period. Following successful defibrillation the FEF registered "C" (yellow) by 60 seconds in all dogs and in 4/5 dogs by 45 seconds. Intratracheal drug administration caused no change in FEF color even when instilled drug was observed to reflux into proximal endotracheal tube.

Relationship between ETCO2 and FEF during CPR is depicted below.



Discussion

The FEF rapidly displayed changes in ETCO2 during actual CPR in this dog model. FEF colors corresponded reliably to IR capnometric data with zone "C" (yellow) reflecting ETCO2 values associated with good prognosis for recovery from cardiac arrest. The FEF responded to restoration of spontaneous circulation as quickly as did the invasive hemodynamic monitors used in our experiment. Concerns that systemic sodium bicarbonate and intratracheal ACLS drugs would affect interpretation of the FEF were not supported by our observations. Humidity collecting in the device caused a slow increase in apparent FiCO2 thus narrowing the color change occurring between inspiration and expiration. While this lessened the visual impact, the relationship between IR ETCO2 and FEF color was unchanged during the course of our experiment (45-60 min.). ETCO2 > 25 mmHg did not change the already bright yellow color of the FEF. Inclusion of a separate color change indicator for hypercarbia would enhance the FEF's usefulness as a monitor of ventilation. Additionally, owing to it's relative expense and limited reusability, use of the FEF is best justified in the acute resuscitation setting (hospital or field), with operating suites and intensive care units better served by dedicated capnography.

Overall, many limitations on ETCO2 detection have been overcome by the development of the FEF. Results from our study show that the FEF reliably reflects ETCO2 during actual CPR. Neither humidity nor standard ACLS resuscitative maneuvers introduced ambiguity into interpretation. Therefore, use of the FEF can provide additional valuable data to assess effectiveness of cardiopulmonary resuscitation.

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Title: **DESFLURANE, ISOFLURANE, AND HALOTHANE PHARMACOKINETICS IN HUMANS**

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Introduction. Desflurane is a new inhaled anesthetic with small blood/gas and tissue/blood partition coefficients (1,2). Recovery from anesthesia and washin and washout are remarkably rapid in animals (3,4). Desflurane also strongly resists biodegradation (5). If these apply to humans, they predict that desflurane will washin and washout more rapidly than other agents, and all the desflurane taken up during anesthesia can be recovered. We confirmed these predictions in the following studies.

Methods. With approval from our institutional Committee on Human Research and written consent, we studied 8 healthy male volunteers [age: 25±5 years (mean±SD); body weight: 75.7±6.8 Kg]. Basal anesthesia was with thiopental and midazolam. Tracheal intubation and controlled ventilation maintained normocapnea. N_2O (65%-70%) washin was measured for 30 min. We then gave 1/3 MAC desflurane, isoflurane, and halothane in 60%-65% N_2O concomitantly for 30 min. We measured inspired (FI), end-tidal (FA), and mixed-expired (FM) anesthetic concentrations and ventilation (VE). We calculated washin (FA/FI) and uptake [(FI-FM)VE]. We measured FA, FM, and VE for 5-7 days of washout, and calculated washout as FA/FA0 (where FA0 is the last end-tidal concentration during washin) and elimination as (FM*VE). Washout of N_2O was measured for 10 min after 150 min of washout of the volatile anesthetics. Time constants of the volatile anesthetics were estimated by fitting 5-compartment exponential equations to the washout data. Using mass balance, we calculated the recovery of anesthetics and thereby metabolism as a fraction of the volume of the individual anesthetic taken up. We used analysis of variance with repeated measures, and Newman-Keuls test to determine differences among anesthetics.

Results. Washin and washout was most rapid with desflurane, followed by isoflurane and halothane ($p<0.05$)(Figure 1,2). Although isoflurane washed in more rapid than halothane, washout did not significantly differ. N_2O washed in more rapid than desflurane but washout was similar. The 5-compartment equation fitted better than 4-compartments for all of the cases (F ratio test). Except for the first compartment, time constants for desflurane were shorter than for the other agents ($p<0.05$)(Table 1). No difference in recovery was found for desflurane (105±25%) versus isoflurane (102±13%). Recovery of halothane (64±9%) was less than with desflurane and isoflurane.

Discussion. As predicted from solubility and animal studies, washin and washout of desflurane were more rapid than that of isoflurane or halothane in humans. The concentration effect explains the more rapid washin of N_2O despite the similarity in solubility with desflurane. The less rapid washout of N_2O probably resulted from the longer (180 min) exposure. The closeness of halothane and isoflurane washout is explained by the greater metabolism of halothane. Previous studies indicated that the 1st, 2nd, 3rd, 4th and 5th compartments represent the lungs, vessel rich group (VRG), muscle group (MG), a compartment composed of intertissue diffusion and fat group (FG), respectively (6). Given the smaller time constant for the VRG, we predict that cerebral washout of desflurane is more rapid than that of isoflurane and halothane and thus, that the recovery from anesthesia with desflurane will be more rapid than from isoflurane and halothane both because of a more rapid clearance from the alveoli and from the brain. The mass balance indicates that desflurane resists biodegradation by humans as much as does isoflurane. This with the smaller time constant for the fat group (*i.e.*, more rapid decay in the terminal portion of the elimination curve), suggests that desflurane may have little, if any, toxic potential.

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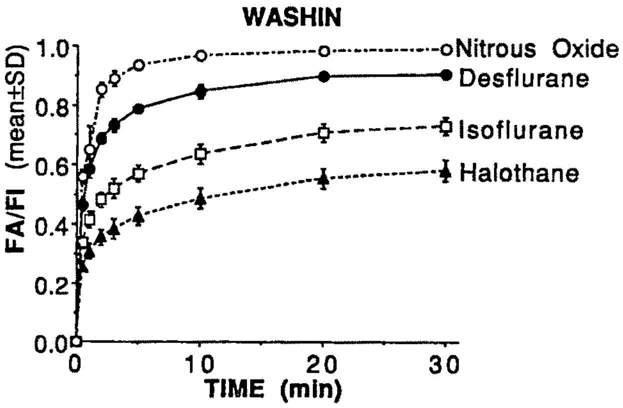
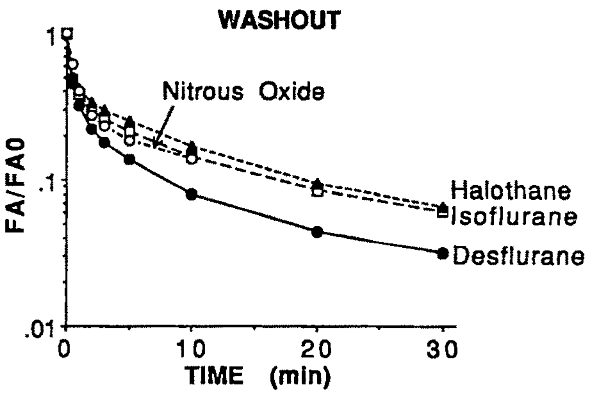
Table. Time Constants (min) for 5 Compartments

Comp.	Desflurane	Isoflurane	Halothane
1st (lungs)	0.44±0.04*	0.38±0.06†	0.31±0.07
2nd (VRG)	5.8±1.6*	8.7±2.1	9.3±1.2
3rd (MG)	49±22*	80±26	85±14
4th	300±110*	480±130†	550±120
5th (FG)	1350±230*	2110±320†	2550±380

values are mean ± SD
* indicates significant vs. isoflurane and halothane ($p<0.05$)
† indicates significant vs. halothane ($p<0.05$)





Title: **STIMULATION MODIFIES THE CARDIOVASCULAR EFFECTS OF DESFLURANE IN HUMANS**

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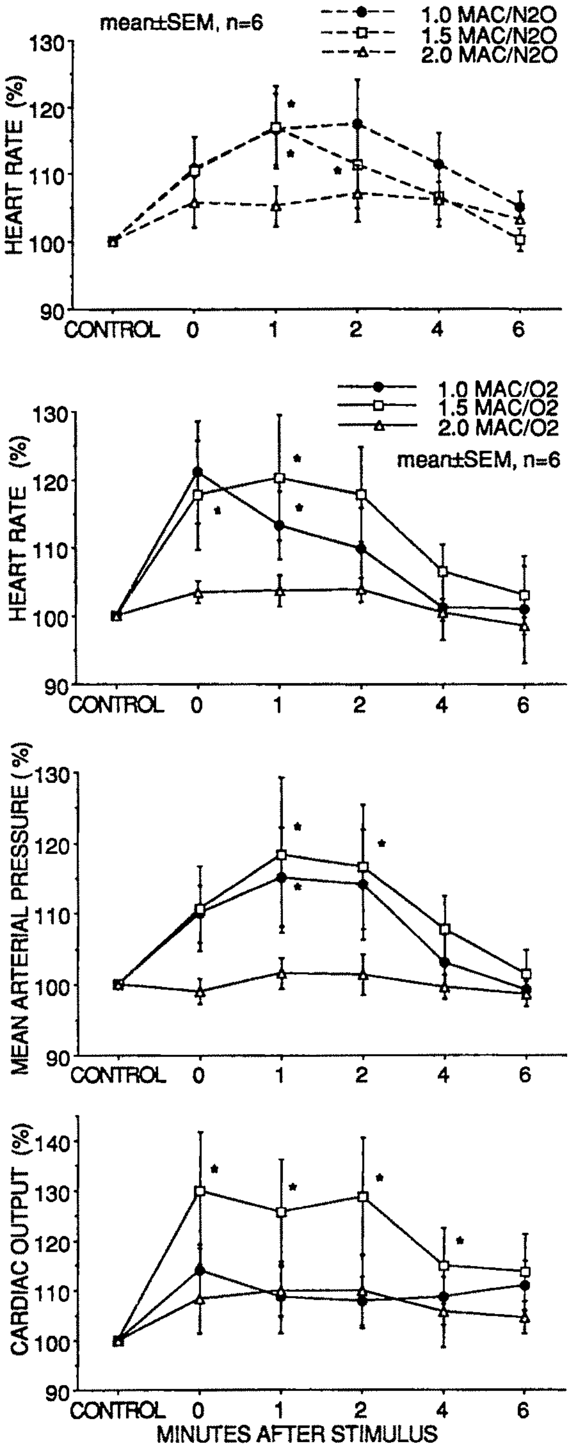
Introduction. Desflurane is a new inhaled anesthetic with cardiovascular properties similar to those of isoflurane in both animals and humans. One limitation to the effectiveness of isoflurane is its weak ability to suppress the circulatory response to pain. Accordingly, we examined whether desflurane suppressed the circulatory response to stimulation of the ulnar nerve in humans.

Methods. With approval from our institutional Committee on Human Research and written consent, we studied 6 healthy male volunteers in whom arterial and pulmonary artery catheters were placed. Anesthesia was induced and maintained with desflurane. The trachea was intubated and ventilation controlled to produce normocapnea. Studies were conducted at 1.0, 1.5, and 2.0 MAC of desflurane in O_2 and in O_2 plus 60% N_2O. After 20 min at each level, the ulnar nerve was stimulated with 50, 100, and 200 Hz impulses sufficient to produce a supermaximal contraction of the thenar muscles. Each stimulus was applied for 5 sec with a recovery time of 10 sec. We measured cardiovascular variables before stimulation (control) and then 0, 1, 2, 4, and 6 min after 200 Hz. We performed analysis of variance with repeated measures and Newman-Keuls test and accepted $p<0.05$ as significant.

Results. Desflurane at 1.0 or 1.5 MAC did not prevent increases in arterial blood pressure or heart rate in response to stimulation, but desflurane at 2.0 MAC limited such responses (N_2O results for the first figure; O_2 results for the next 3). However, the results 2 MAC desflurane and O_2 may be misleading for heart rate because this level of anesthesia produced tachycardia (102±5; mean±SE) in the control state. In five of six of the anesthetic combinations, the initial response of the heart rate was to increase more than blood pressure. There was no dose-related suppression of the cardiac output response to stimulation. With desflurane plus N_2O, cardiac output increased at all levels; with desflurane in O_2, output increased at 1.5 MAC but not at other levels. As indicated by the standard error bars surrounding each mean value, the response was irregular. For most variables at most levels, the variables returned towards or to control levels by six min after cessation of stimulation. Central venous pressure and pulmonary artery blood pressure were unaffected by stimulation.

Discussion.

Our results suggest that desflurane is similar to isoflurane in its ability to limit the cardiovascular response to stimulation. N_2O did little to modify this ability. As opposed to our results for response to ulnar nerve stimulation, the response to surgical stimulation might take one or more forms. First, much of the response we measured returned to or towards normal by 6 min after cessation of stimulation. This might have resulted from absence of stimulation or from accomodation to stimulation. If the latter were true, then clinically we would not expect to see much response to surgical stimulation after an initial, transient, response. Second, surgury may provoke a greater and more prolonged response because stimulation is ongoing.



* indicates significant vs. control ($p<0.05$)
Values are % of control

itle: THE RELATIONSHIP OF END-TIDAL TO ARTERIAL CO2 TENSION DURING CEREBROVASCULAR SURGERY IN THE ELDERLY

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Introduction. Aging is known to affect pulmonary function [1]. Whenever PeCO2 values are used to estimate PaCO2, knowledge of the gradient (Pa-eCO2) is important, especially when direct access to the arterial circulation is not possible. To examine the influence of aging on Pa-eCO2, we compared the relationship of PeCO2 and PaCO2 in 44 patients undergoing cerebrovascular surgery.

Methods. After institutional approval and informed consent, patients undergoing elective carotid endarterectomy (n = 27) or resection of cerebral arteriovenous malformation (n = 17) were included in the research protocol. Anesthesia was induced with thiopental 4 mg/kg and endotracheal intubation facilitated with a non-depolarizing muscle relaxant. Anesthesia was maintained with either 0.5% halothane or 0.75% isoflurane in nitrous oxide and oxygen. Standard capnography and arterial blood gas analysis were employed using routine calibration procedures. Three to 7 simultaneous measurements of PeCO2 and PaCO2 were performed in each patient. For the purpose of analysis, patients were divided into three groups: Young (20 - 44 yrs), Mid-age (45 - 65 yrs) and Elderly (>65 years). No patient had clinically significant chronic pulmonary disease. Physiological variables were compared by one-factor ANOVA or by linear regression. For each individual patient the relationship of PeCO2 and PaCO2 was examined. The threshold for significance was taken as $p < 0.05$. All values are expressed as mean ± SE.

Results. Using the baseline measurement for each patient the relationship of PeCO2 and PaCO2 is shown in Figure 1. For the total sample of 227 measurements, the relationship was PeCO2 = 0.74 PaCO2 ± 2.31, $r = 0.845$, $p < 0.001$. The mean r value for the individual within-subject correlations was influenced by age group, with better correlations existing in younger patients than the mid-age and elderly patients (0.95 ± .02 vs. 0.78 ± .07 vs. 0.67 ± 0.01). Physiological variables are shown for the 3 groups in Table 1. For all 227 measurements Pa-eCO2 was 6.1 ± 0.2 mmHg.

Discussion. Pulmonary function becomes progressively compromised with increasing age, involving respiratory mechanics, lung volumes and gas exchange [1]. This study shows that there is a significant widening of the Pa-eCO2 gradient in mid-age and elderly patients compared to younger controls. In contrast to a previous report [2], we observed a good correlation between PeCO2 and PaCO2 in individual patients, but this relationship was weaker in the elderly. Use of PeCO2 has replaced direct arterial sampling in many clinical circumstances. In many neurosurgical patients it is of critical importance to accurately gauge the level of hypocarbia [3]. Use of PeCO2 values to estimate PaCO2 should take into account the age of the patient.

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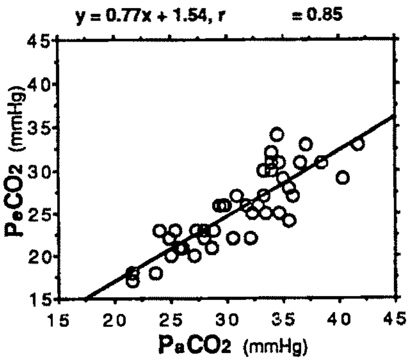

Figure 1

**Relationship of PeCO2 and PaCO2
(n = 44, p < 0.001)**

Table 1. Effect of age group on Pa-eCO2 and other physiological variables

	Young n = 14	Mid-age n = 19	Elderly n = 11
Age	31±2	59±1	76±1
Pa-eCO2	4.5±0.6	6.1±0.4*	6.9±0.6*
PaCO2	28.4±1.5	31.9±1.0*	32.8±1.1*
PeCO2	24±2	26±1	26±1
Temperature	35.4±0.2	35.3±0.2	35.6±0.3
MAP	77±3	88±2*	104±4*

*Significantly different from young group.

Title: AN EVALUATION OF METOCLOPRAMIDE IN CONJUNCTION WITH DROPERIDOL FOR ANTIEMETIC PROPHYLAXIS IN OUTPATIENT LAPAROSCOPY.

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Introduction: Nausea and vomiting are the commonest anesthetic related side-effects after general anesthesia for outpatient laparoscopy. They may contribute to prolonged recovery room stay or overnight admission. Droperidol (**D**) in a dose of 10-20 mcg/kg, is thought to reduce the incidence of emetic symptoms (**ESx**) after laparoscopy performed under general anesthesia (1). Metoclopramide (**M**) is a non-sedating dopaminergic blocker with central and peripheral sites of action. Its use as a premedicant has been advocated as possibly synergistic with **D** for antiemetic prophylaxis in outpatient anesthesia (2). However, the combination of the drugs has been disputed (1).

A recent report suggests that **M**, in a dose of 0.15 mg/kg is best given upon arrival in the recovery room and not as a premedicant (3). In order to evaluate this possibility we performed a randomized, single-blinded, prospective study to determine the incidence of emetic symptoms with **M** was given either during or after outpatient laparoscopy.

Methods: Following IRB approval and written informed consent, 40 adult women undergoing outpatient surgical laparoscopy under general anesthesia were recruited for this study. Preoperatively the presence/absence of emetic symptoms (**ESx**) and history of **ESx** with other anesthetics or history of motion sickness was determined. Premedication consisted of fentanyl 1.5 mcg/kg, which was immediately followed with thiamylal for induction. Maintenance of anesthesia consited of nitrous oxide/ enflurane/ oxygen via endotracheal tube, with vecuronium for muscle relaxation. All patients received **D**- 15 mcg/kg and an oral gastric tube to low suction after intubation. No further narcotics were given and all patients had antagonism of residual blockade prior to extubation.

Patients were randomized to four equal groups: Group A received no **M**; Group B received **M** 20 mg after induction in the OR; Group received **M** 20 mg in 250 ml IV fluid over 20 to 30 min upon arrival to the PARR; while Group D received **M**, 20 mg in the OR and another 20 mg in the PARR. All patients received at least 20 ml/kg of IV fluid prior to disharge. All patients were followed by a research nurse, who was unaware of the group assignment (as were the PARR nurses and residents), from arrival to the PARR until discharge. Patients were assessed for the presence/absence of **ESx**: which included: **A** = asymptomatic; **N** = nausea; **R** = retching; **V** = vomitting at half hour intervals until discharge and then the next day by phone.

Demographic data, discharge times, etc. were analyzed by a t-test with a P <0.05. **ESx** were analyzed by an ANOVA with a significance level set at 95%.

Results: There were no statistically significant differences in age, weight, length of surgery, times to eye opening, orientation, ambulation and discharge (data not shown).

ESx for the **PAR** stay and **24 hrs** after discharge are shown in Tables 1 and 2 resp.

TABLE 1: EMETIC SYMPTOMS FOR PARR

Group	A	N	R	V
A	4	5	0	1
B	2*	3	1	4
C	6	3	0	1
D	6	3	0	1

TABLE 2: EMETIC SYMPTOMS FOR 24 hrs

Group	A	N	R	V
A	5*	1	0	4*
B	10	0	0	0
C	9	1	0	0
D	8	2	0	0

Shown above are the numbers of patients with **ESx**. * denotes a significance level of > 95% by ANOVA. For key see methods.

For the **PARR** stay, when all **ESx** were considered (i.e. **N+R+V**), groups A+B had a tendency to do worse, but this difference did not reach statistical significance. However, when Group B was compared to C or D, fewer Group B patients were asymptomatic.

For the first 24 hrs after discharge group A had both fewer assymptomatic patients and a higher incidence of **V**.

Discussion: We were unable to find benefit from **M** based upon the incidence of **ESx** in the PARR. However, there was improvement of **ESx** in all patients receiving **M** in terms of 24 hour followup. Although there was a tendency to fewer **ESx** while in the PARR in groups C and D, this was not significant. Due to the 4 group randomization, and low power of the present study, further patient recruitment will be needed to support a conclusion for the optimal timing of **M** administration for outpatient anesthesia.

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TITLE: PLASMA HISTAMINE WITH INTRASPINAL MORPHINE IN CESAREAN SECTION

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Introduction: Intraspinal morphine use in cesarean section patients is associated with a high degree of pruritus. This study examines the relationship between epidural and intrathecal morphine, plasma levels of morphine and histamine, and pruritus.

Methods: Following Institutional Review Board approval, informed consent was obtained from 12 ASA class 1 patients scheduled for elective cesarean section. Patients were randomly divided into two equal groups. Six patients were given intrathecal anesthesia with bupivacaine 12 mg in 7.5% dextrose with 0.6 mg preservative free morphine. Six patients received epidural anesthesia using lidocaine 2% with epinephrine 1:200,000, and received morphine 5 mg, epidural, after delivery. All patients received lactated Ringers 1500 cc hydration prior to placement of regional anesthesia at L2-3, achieving a T4 sensory level. Samples were obtained via an indwelling antecubital venous catheter at 0, 2, 5, 15 and 30 minutes, and 1, 2, 3, 4, 6, 12 and 24 hours after morphine administration. Histamine samples were drawn into heparinized syringes and immediately placed on ice, then centrifuged at 4°C while morphine samples were collected in EDTA, then centrifuged at 20°C. Unconjugated morphine was analyzed using a radioimmunoassay with a range of 0.8-200 ng/ml. Histamine was measured using radioimmunoassay with a range of 0.3-200 ng/ml. Patients rated itching hourly on a 100 mm visual analog scale (0=none, 100=worst possible). Statistics were performed using independent t-test at $p<0.05$.

Results: Unconjugated plasma morphine levels remained below 0.8(±0.17=1SE)ng/ml in the intrathecal group while it decreased from 14.2-0.25 ng/ml in the epidural group during the study period (Fig 1). Plasma histamine levels did not differ between groups (range 2.5-4.6 ng/ml) until 1 hour. However, at 3, 6 and 12 hours plasma histamine was significantly higher in the intrathecal anesthesia group compared to the epidural group ($p<0.05$) (Fig 2). Peak plasma histamine levels of 6.2(±2)ng/ml occurred at 3 hours in the intrathecal anesthesia group. Patients receiving epidural morphine had maximum itching at 4.3 hours with a severity score of 33 while those receiving intrathecal morphine had maximum itching at 3.3 hours with a severity score of 48 (N.S.).

Discussion: These results show that in cesarean section patients intrathecal morphine 0.6 mg produced a sustained elevation of plasma histamine from 3-12 hours after administration when compared to epidural *morphine* 5 mg. The increased plasma histamine and very low level of plasma morphine after intrathecal *morphine* suggests a central mechanism of action. Intrathecal morphine administration produces a higher cerebrospinal fluid concentration then does epidural morphine.[1] The central neuraxis possesses a histaminergic system,[2] which may be directly or indirectly involved in the systemic histamine elevation. Further studies investigating the mechanism of plasma histamine elevation are indicated. Although a trend towards earlier, more severe itching in the intrathecal group exists, neither the timing, severity, nor correlation with plasma morphine or histamine levels reached significance.

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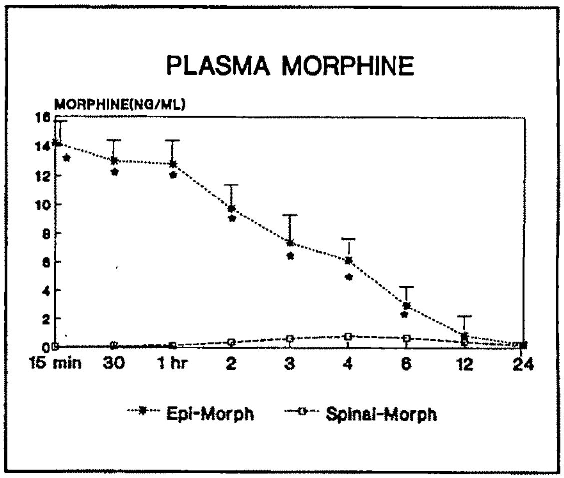

Figure 1.

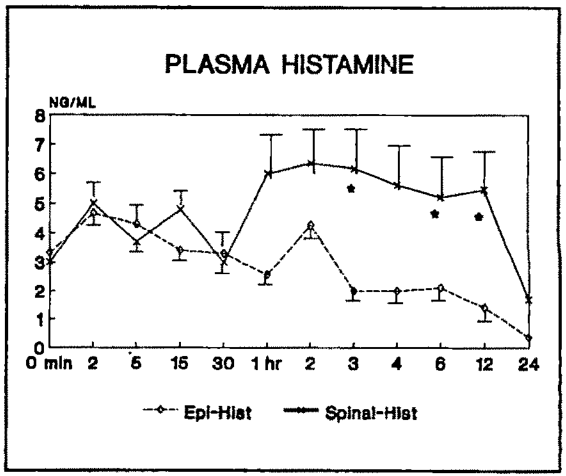

Figure 2.

Title: **THE SEDATIVE AND VENTILATORY EFFECTS OF DEXMEDETOMIDINE IN RABBITS**

Authors: **MH Zornow**, MD, **ML Spooner**, BS, **AE Bloom**, **PJ Kelly**, and **MS Scheller**, MD

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Introduction: Dexmedetomidine (DMET) is a potent and selective alpha-2 adrenergic agonist which is known to possess anesthetic and analgesic properties.[1,2] It has been speculated that DMET may be able to produce these desirable effects without the respiratory depression produced by narcotics or volatile anesthetics.[3] This study examined the effects of increasing doses of DMET on respiratory rate (RR), $PaCO_2$, PaO_2, and Sedation Score (SS) in rabbits.

Methods: Following approval by the Animal Care Committee, 21 New Zealand white rabbits weighing 2.8±0.5 kg were studied. Following infiltration with 0.1 ml of 0.25% bupivacaine, catheters were inserted into an ear artery and vein. Animals were left undisturbed for a period of 5 minutes and then control measurements of the monitored variables (RR, $PaCO_2$, PaO_2, and SS) were made. Sedation was assessed by assigning scores of 0 (normal), 1 (abnormal), or 2 (absent) to righting reflex, response to paw pressure, respiratory pattern, pupillary light reflex, startle response, corneal reflex, and spontaneous movement. The SS therefore could range from 0 (normal) to 14 (severely obtunded). The animals then received DMET (20, 80, or 320 µg/kg) or saline as a 10 minute infusion. Monitored variables were recorded at 5, 15, 30, and 60 minutes after completion of the infusion. Changes in the monitored variables following the infusion of DMET or saline were calculated by subtracting corresponding control values. Data were analyzed using a 2-way ANOVA followed by Dunnet's test for multiple comparisons vs. the saline group when indicated. Significance was assumed for $p < 0.05$.

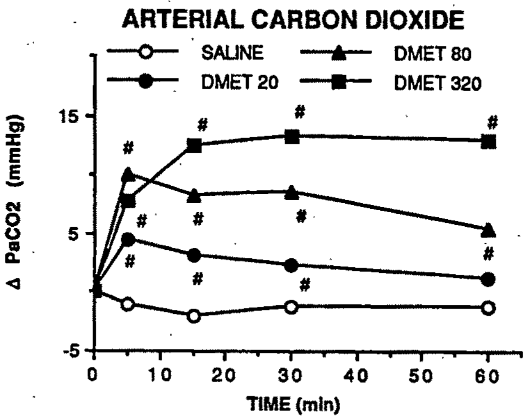

Figure 1. Effects of DMET (20, 80, 320 µg/kg) and saline on PaCO2. #= p <0.05 vs saline group.

Results: Administration of DMET had a significant ($p<0.001$) effect on oxygenation. PaO_2 decreased by means of 32 and 34 mmHg in those animals which had received 80 and 320 µg/kg of DMET at 5 minutes post-infusion. Similar, although less profound, reductions in PaO_2 were seen in those animals which received 20 µg/kg DMET. RR decreased significantly to 65%, 45%, and 49% of control in those groups receiving 20, 80, and 320 µg/kg DMET respectively at 5 minutes post-infusion. DMET had significant effects on $PaCO_2$ and SS as shown in Figures 1 and 2.

Discussion: DMET can reduce halothane MAC by greater than 90% in rats and dogs. This study demonstrates that DMET also possesses sedative and analgesic properties in the rabbit. As evidenced by dose-dependent increases in $PaCO_2$ and decreases in respiratory rate, DMET is a respiratory depressant in this species.

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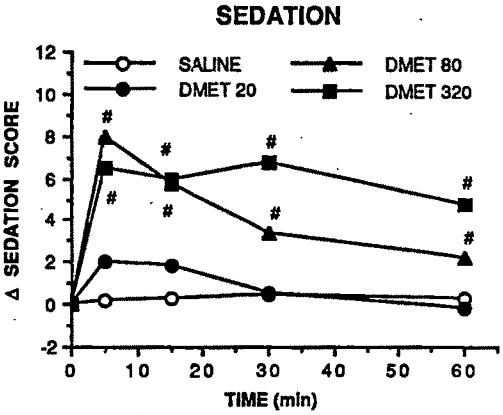

Figure 2. Effects of DMET (20, 80, 320 µg/kg) and saline on Sedation Score. #= p <0.05 vs saline group.

Title: THE EFFECT OF HALOTHANE ON ARRHYTHMOGENIC RESPONSES INDUCED BY SYMPATHOMIMETIC AGENTS IN SINGLE RAT HEART CELLS

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Introduction. The combination of catecholamines and halothane (H) has long been recognized as arrhythmogenic. However, the mechanism of this interaction remains unclear.1 Several mechanisms of arrhythmia production have their origins in phenomena which occur in individual cardiac cells. That is, such phenomena occur independently of cell-to-cell conduction (impulse propagation) even though they may contribute to altered cardiac conduction. Spontaneous contractile waves in cardiac cells are distinct from normal synchronous contractile activity and are caused by localized Ca++ release from the sarcoplasmic reticulum (SR).2 Such waves are observed in resting rat myocytes at physiologic extracellular Ca++ concentrations. Stimulation of the myocytes at 60 beats/min typically suppressed these contractile waves. Environmental changes which lead to appearance of waves between stimulated beats indicate an increase in spontaneous Ca++ release from the SR and is usually associated with an increase in total intracellular Ca++. These inter-beat waves (IBWs) can attenuate the subsequent beat and in some circumstances lead to the generation of spontaneous action potential. Thus, they have arrythmogenic potential.3 Triggered activity is another arrhythmogenic mechanism which can be observed in single cardiac cells. Triggered activity includes early aftercontractions (EACs) and late aftercontractions (LACs), the mechanical correlates of the similarly named depolarizations.4 LACs are contractions, usually much smaller than normal, which occur when a sequence of stimulated beats ceases. EACs occur during the relaxation phase of a normal contraction and may appear as an ectopic contraction, or as a failure of the initial beat to completely relax, or both. To determine whether halothane-catecholamine arrhythmias might be initiated by such cellular events, we investigated the effect of combinations of H and sympathomimetic agents (SYMs) on single rat heart cells. Isoproterenol (ISOP), norepinephrine (NE), and phenylephrine (PE) were the SYMs used since they possess β-, mixed, and α-adrenergic properties, respectively.

Methods. The protocol was approved by the institutional animal care and use committee. The length of single, freshly isolated, Ca++-tolerant rat ventricular myocytes was continuously measured at 36.5° C as previously described.5 Cells were sequentially exposed to a SYM, then H(0.30mM, approx. 0.9 vol%) plus the SYM, then again to the SYM alone. Other cells were exposed to H alone first, then to the combination. Series of 60 beat trains at 1 beat/sec were induced by field stimulation. Each train of beats was scored for the presence of EACs, LACs, and IBWs. In some cases, stimulation was not interrupted and EACs and IBWs alone were measured. All results were taken after a steady state in the new solution was achieved.

Results. The table shows the incidence (# of trains with events/total # of trains) of these arrhythmogenic phenomena in the presence of each of the SYMs, with and without H. H either reduced or did not change the frequency of EACs, LACs, and IBWs. H did not alter the response to SYMs at lower concentrations than those in the table, which produced little triggered activity or IBWs. At higher concentrations of the SYMs, the cells went into uncontrollable contractile activity, which was not reversible. H alone did not induce LACs, EACs or IBWs under the conditions of this study.

		ISOP ($1x10^{-7}M$)	NE ($1\text{-}3x10^{-7}M$)	PE ($5\text{-}10x10^{-6}M$)
IBWs	No H	19/25	20/59	0/32
	H	*13/30	15/51	0/24
EACs	No H	17/25	24/59	10/32
	H	*9/30	14/51	6/24
LACs	No H	8/16	18/33	0/12
	H	5/15	8/26	0/11

*Different from no H (P less than 0.05) by chi-squared analysis

Discussion. At the single cell level, our results show clearly that H does not increase SYM-induced triggered activity. Furthermore, halothane appears to reverse the arrhythmogenic phenomena induced by ISOP and NE. This antiarrhythmic effect of H was not seen in cells exposed to PE. Maze et al has demonstrated the dominant role of α (as opposed to β) receptor in mediating the H-SYM arrhythmogenic interaction in dogs.6 The ability of H to attenuate β-induced arrhythmogenic events at the cellular level may relate to their observations. Others have demonstrated that H decreases automaticity.7,8 On the basis of our results, triggered activity or IBWs are also an unlikely mechanism of the arrhythmias associated with the combination of H and SYMs. Thus, alterations in cardiac conduction (e.g., re-entrant phenomena) appear to be the probable cause of this arrhythmogenic interaction.

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